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The extension and diversification of physiological publication has caused the urge for the establishment of new specialized journals or the restriction in scope of existing ones. It becomes inexpedient for a journal to diversify its contents more and more in an attempt to serve an expanding subject completely. A far greater variety of subjects must be included than are of direct interest to individual workers or to specialized laboratories. This increases the cost of those articles that are desired to such an extent that an individual's subscription support of a journal may be discontinued and dependence placed upon libraries and other repositories. This is not altogether desirable and to a considerable extent may be offset by the formation of specialized organs of publication, provided they serve a field that has a considerable permanent interest and a large body of active workers.

Additional journals, hence, appear to be an inevitable consequence of the expansion and specialization of a field. New scientific knowledge gained from research is sterile without some degree of publication; with limited or restricted publication it fails to achieve its highest objectives. Indeed, unless it is published in media that are accessible to scientists throughout the world, it may become essentially lost and useless. Much of modern physiological research demands enormous expenditures for complex apparatus, instruments, equipment and laboratories, for highly trained technical and professional personnel, and for planning and administration. Few would question the justification of large expenditures of public and private funds for such support. The essential corollary, that of adequate facilities for publication, has not been implemented to the same extent. Yet it is as essential to the increase and diffusion of scientific knowledge as are the researches that originate that knowledge.

The AMERICAN JOURNAL OF PHYSIOLOGY, founded in 1898 and now in its one hundred and fifty-fourth volume, exemplifies the amazing development, extension and specialization of physiological research during that time. This journal currently publishes more than 350 papers a year covering almost all aspects of experimental physiology. This is only a part of the total yearly increment. The JOURNAL OF APPLIED PHYSIOLOGY has accordingly been initiated by the American Physiological Society in order to better serve the growing and more specialized needs of this field of research. It is intended to complement and not to compete with the older journal of the Society. The policies of each journal will be kept in close harmony with those of the other through the agency of the Board of Publication Trustees. The Editorial Board is charged with the responsibility of carrying out these policies and of maintaining high standards of quality. It is planned to add an advisory editorial board of outstanding physiologists outside of North America to encourage the contribution of research papers from abroad.

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*Foreword*

THIS IS THE FIRST NUMBER of a new Journal intended to serve the needs of one of the fields of physiology. That field is designated as 'applied' physiology and perhaps requires some delimitation. The application of the facts, principles, laws, methods and technics of physiology, the mother of the biological sciences, is not at all new, but is as old as the science itself. In connection with this Journal the term 'applied' will broadly connote human physiology, with particular emphasis on man in relation to his environment and the adaptations his physiologic mechanisms show in response to the many and varied stresses imposed by man's environments. The terms 'stress' and 'environment' will also be interpreted broadly to include work, exercise, industrial, military, climatic, nutritional and even social and economic factors, as well as those that seem, in the shadow of our present lack of knowledge at least, to arise from within the body itself. For example, physiological aspects of heredity, of aging and the aging process, and of metabolism will come within the scope of this Journal. At the present time the stresses imposed upon man's mechanisms for homeostasis by climate, altitude, temperature and work are receiving much intensive study by physiologists and the need of another medium for the publication of such studies is urgent. Research emphasis, however, may shift in the future and the scope of the JOURNAL OF APPLIED PHYSIOLOGY has purposely been set along broad lines to accommodate wide shifts in interest. The term 'physiology' will be interpreted rather strictly in delimiting the field of the Journal.

Over the past forty years the number of medical and biological journals has increased a hundred-fold and still continues to increase. It would seem to be incumbent upon those responsible for inaugurating a new journal to set forth the reasons which, in their opinion, justify calling upon the groups served to support the publication both by the contribution of articles, and by subscription and use.



The extension and diversification of physiological publication has caused the urge for the establishment of new specialized journals or the restriction in scope of existing ones. It becomes inexpedient for a journal to diversify its contents more and more in an attempt to serve an expanding subject completely. A far greater variety of subjects must be included than are of direct interest to individual workers or to specialized laboratories. This increases the cost of those articles that are desired to such an extent that an individual's subscription support of a journal may be discontinued and dependence placed upon libraries and other repositories. This is not altogether desirable and to a considerable extent may be offset by the formation of specialized organs of publication, provided they serve a field that has a considerable permanent interest and a large body of active workers.

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July 1948

# Temperature Changes in Blood Flowing in Arteries and Veins in Man<sup>1</sup>

H. C. BAZETT, L. LOVIE, M. NEWTON, L. EISENBERG, R. DAY, AND R. FORSTER II, *From the Department of Physiology, University of Pennsylvania, Philadelphia, Pennsylvania*

THE INTERCHANGE of heat between arteries and adjacent veins was described first by Claude Bernard (1), who made many measurements of arterial temperatures in animals and described moderate cooling of arterial blood in large vessels such as the femoral artery in the dog. The existence of this factor in the economy of heat exchange has long been known (2-4). However, only recently has it been realized that cooling of blood in the arteries can be great enough to be of considerable practical importance.

In order to meet war problems methods of measurements of the heat exchange of the hand and foot were devised (5). These were later modified and extended by Forster *et al.* (6), who combined estimates of heat exchange with measurements of blood flow. The latter data showed that considerable precooling of arterial blood in passage to the hand or foot had to be assumed in order to explain the observed heat exchanges. The same hypothesis was essential also to explain bizarre temperature changes, which were sometimes observed in the data of Mendelson *et al.* Some of these data will be discussed in a subsequent paper. In order to confirm or deny this hypothesis direct measurements of intravascular temperatures were made at the O.Q. M.G. laboratory in 1945 by a combined group of workers from this laboratory and from the University of Pennsylvania. The experiments were later continued at the University.

The initial experiments consisted in sampling the temperatures existing in peripheral arteries and veins of the arm under different conditions. Needle thermocouples were used, which proved difficult to maintain within an artery with certainty for any length of time. For the later experiments thermocouples protected by a fine plastic tube were employed. These can be threaded through a fine needle for considerable distances up a vessel, so that their presence within the vessel is assured. The plastic tube has non-wetting properties and does not cause clotting, so that the couples may be

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<sup>1</sup> We would like to acknowledge gratefully assistance from the Life Insurance Medical Research Fund in meeting part of the expenses of this work, as well as from a grant from the Office of Naval Research which aided the development of the plastic tube.

left in place for hours. Consequently the later experiments have concerned mainly the change in vascular temperatures that result during adjustments to new conditions.

### METHODS

The needle thermocouples consisted of hypodermic needles of 0.46 to 0.65 mm. external diameter threaded with an enamelled silk-covered constantan wire of 0.08 to 0.1 mm. diameter, and also with a copper wire of 0.06 mm. diameter insulated only with enamel. Both wires were soldered to the needle orifice. The fine wires extended up into the glass barrel of a 2 ml. syringe, where they were separated by spaghetti tubing and

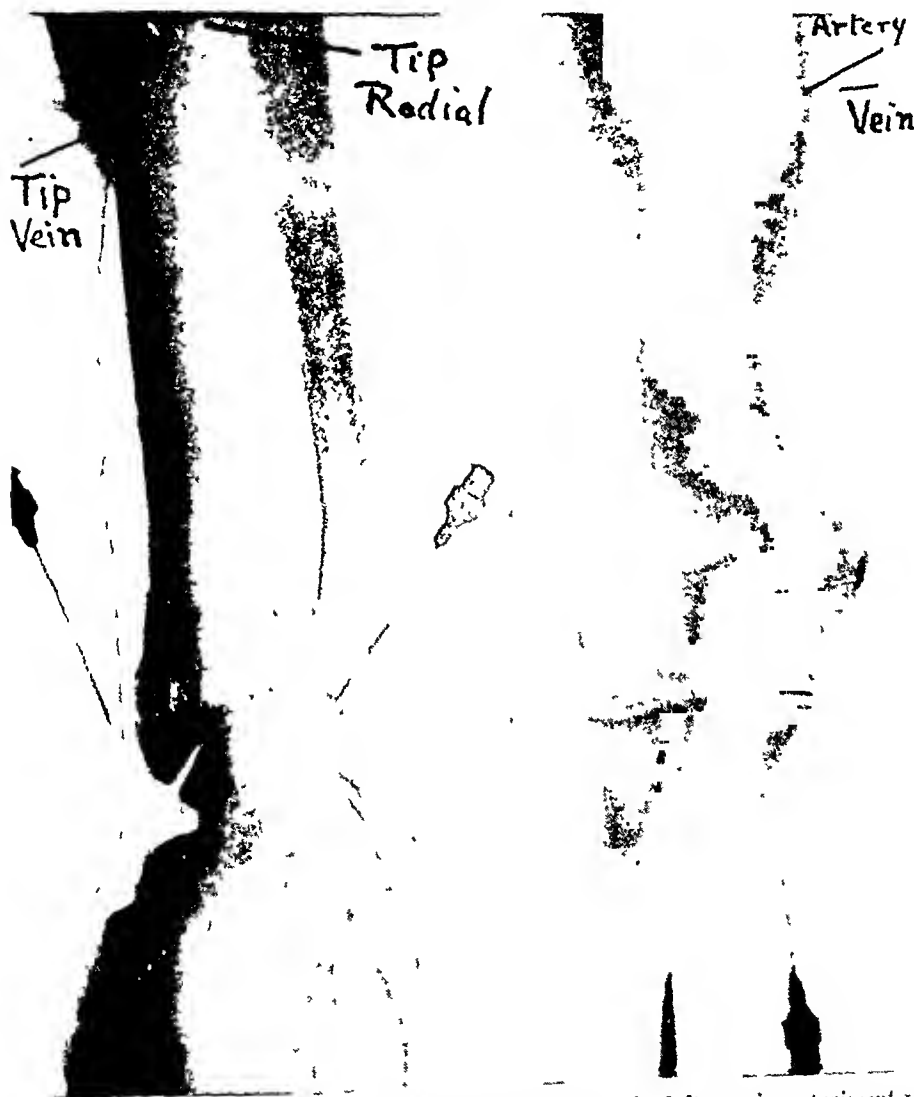


Fig 1. X-RAY PHOTOGRAPHS OF THE THERMOCOUPLES in the left arm in experiment 11. At the left, the couple in the wrist vein may be seen coursing up from the entrance through the skin distal to the wrist joint to the point marked 'tip'. The radial couple can be distinguished in the original photograph ending more proximally, as is also indicated in the figure. The photograph to the right indicates more clearly the couples in the brachial artery and median basilic vein. The needles may be seen withdrawn from the skin and lying free on proximal parts of couples.

soldered to heavier wire. The heavy wire was gripped by a cork inserted into the open proximal end of the syringe barrel. The reference junction was kept in a thermos flask at any convenient temperature.

The plastic-covered thermocouples were made in various sizes from an outside diameter of 0.4 to 0.6 mm. The wires used were the same as those described above, though in most cases the silk insulation of the constantan wire was discarded in order to simplify their manufacture. If the wires be carefully treated, the insulation of the two wires with enamel seems adequate. This is not the case within needles, where the metal cover greatly facilitates short circuits. The plastic-covered couples are made in the following manner. Tubing of a polyvinyl plastic<sup>2</sup> is drawn out for the narrowest couples until its external diameter is 0.4 mm., when its internal diameter is about 0.2 mm. It is baked at this length for one or two days at a temperature of about 105°C., and becomes increasingly rigid the longer it is baked. Lengths up to 28 cm. have been threaded by making a thermocouple of Y shape and using the tail of the Y to draw the remainder through the tube. After the couple and the limbs of the Y have been threaded, the tail can be removed. A ligature at the proximal end of the tube fixes the wires and the couple is arranged to lie just within the distal lumen. The distal orifice is plugged with beeswax. The proximal ends of the fine wires are soldered to heavier wire and are bound with adhesive tape.

The finer plastic tubes may be introduced into the vessels through hypodermic needles of special tubing with a light wall. The smallest tubing has been 0.71 mm. O.D. and 0.59 mm. I.D. For easier threading the needle tubing has been soldered into hubs with the proximal end protruding slightly beyond the end of the hub. The plastic tubing and needles are those developed by Peterson and Risman (7) for use in blood pressure recording. They have been merely adapted to the present use. The needles are withdrawn along the plastic tube after this is in the artery.

*Technic of Measurement.* Except for a few early experiments the couples have been connected to Kipp and Zonen microgalvanometers of 0.2 second period for photographic recording, or else to a mirror galvanometer with reflectors and enclosed scale. Selective switches have allowed more than one thermocouple to be attached to a single galvanometer. Surface temperature measurements have been made by copper-constantan couples of wire of 0.13 mm. diameter. To measure tissue temperatures the needle couples have been inserted into the tissues and approximate corrections for errors due to conduction have been made (4). Rectal temperatures have been taken either by clinical thermometers or thermocouples. For the latter a larger plastic tube has been employed with constantan wire of 0.1 mm. and copper wire of 0.2 mm. diameter to form the couple, which has been inserted to a depth of 15 cm. or more.

All the couples have been standardized under the conditions of use over the range for which they have been employed (commonly within 24 hours of their experimental use). Sensitivity has been reduced when necessary by the introduction of additional resistances.

The introduction of needle couples into an artery can often be recognized by both operator and subject by a sudden reduction in the resistance of the needle; the subject may also recognize a characteristic ache, particularly when large needles are used. This ache is generally absent when small needles are used for large arteries. The temperature of the thermocouple under cool conditions shows a sudden jump of 1.0 to 1.5°C. as the needle pierces the arterial wall.

<sup>2</sup> Irvington Varnish and Insulator Co., Irvington, N. J.

A similar procedure may be used for introduction of the plastic tubes into veins, if they are introduced centripetally. Even in arteries the tubes can be introduced more easily centripetally, since when passed peripherally the tip may catch in a small branch. The couples may readily be demonstrated by x-rays after introduction.

*Conditions of the Subjects.* The subjects usually sat quietly for some while in a cooled or warmed room. In the experiments with plastic tube couples the times used were extended to more than 6 hours. In these experiments also local cooling or heating of the limb peripheral to the couples was employed.

## RESULTS

### *Observations in the initial experiments with needle thermocouples*

In the initial experiments sample measurements of radial, brachial or venous blood temperatures were made with a single needle thermocouple introduced successively into different vessels. Other couples were used to record surface temperatures in the hand and over the points at which the vessel temperatures were sampled. Usually only one, or at most two, galvanometers were employed, so that few observations were exactly contemporaneous. The subjects were seated usually about 20 minutes to  $1\frac{1}{2}$  hours before the readings were taken so that temperatures changed slowly, and comparisons of different vessels with one another were not impaired seriously. The subjects were lightly clad (light shirt and trousers) and when in a cold room sat until shivering threatened to be troublesome. The data obtained in these early experiments are shown in table 1, where the duration recorded is the time from the beginning of exposure to the measurement of the radial temperature. Measurements of brachial and venous temperatures usually followed immediately. In *experiment 4* measurements were also made of tissue temperature by transfixion of the thenar eminence with the same needle thermocouple that was used for the vascular measurements. The gradients are indicated in figure 2, which shows also the vascular temperature.

In this experiment the radial temperature was so low as to cause doubt as to the position of the needle in the artery, even though a large arterial hematoma had formed. A second puncture somewhat proximal to the first was therefore made by Dr. John Talbott. His great experience in such punctures was valuable and we are much indebted to him for his assistance. In spite of further cooling of the hand a somewhat higher (though comparable) value was obtained and a second hematoma gave evidence of puncture of the vessel. The rise in temperature appeared anomalous until later experiments demonstrated that any compression of the vessels distal to the point of measurement could produce such a result through interference with the return of cooled blood in venae comites. The initial hematoma lying distal to the second puncture should have had precisely this effect.

The data in table 1 are self-explanatory. It is obvious that while individual differences doubtless exist, the temperatures recorded in vessels,

whether arterial or venous, are lower the colder the environment and the longer the time of exposure to such cold conditions. The fall of temperature between the brachial and radial varied from  $0.8^{\circ}\text{C}.$  at a comfortable room temperature to  $8.5^{\circ}$  in the cold, i.e., from about  $0.03^{\circ}$  to  $0.35^{\circ}$  per cm.

TABLE I. TEMPERATURES IN ARTERIES AND VEINS OF ARMS ESTIMATED WITH NIELLE-THERMOCOUPLES

SUBJ.	TIME	ROOM TEMP.	BRACH. ART.	RADIAL ART.	ELBOW VEIN	SURFACE TEMPERATURES			RECTAL <sup>1</sup>	EST. GRAD. <sup>2</sup>
						Elbow	Wrist	Aver. hand		
	min.	°C.	°C.	°C.	°C.				°C.	°C.
D	35	4	—	28.9	—	—	—	14.5	—	—
H	51	6	—	25.1	27.8	28.8	19.0	14.8	37.05 A	2.3
B	00	7.2-11.9	33.9	25.4	32.0	—	24.6	15.1	36.7 B	—
									36.4 A	
B	95	9	—	21.5	—	—	—	13.9	36.9 B	1.4 <sup>3</sup>
	103	0	—	22.2	—	26.0	—	—	36.8 A	1.6
F	20	9	—	28.7	34.3	32.4	25.0	21.1	37.5 B	1.5
B	56	10	—	28.1	32.5	20.0	24.4	16.1	37.3 B	1.1
									37.0 A	
D	55	13.0	35.5	29.1- 34.3	30.1 (hand warmed)	26.8	22.8	19.4	37.0 B	—
									36.4 A	
M	45	13.6	35.8	30.5- 34.2	34.8 (hand warmed)	—	—	—	37.6 B	—
									37.5 A	
D	105	22.0	36.3	35.5	33.2	30.9	28.4	27.9	36.7 A	—
B	30	22.0	37.1	36.2	32.6	33.1	32.9	32.2	37.1 A	—

<sup>1</sup> A, before; B, after.    <sup>2</sup> Estimated gradient across arterial wall.

<sup>3</sup> In this experiment measurements of tissue temperature in the thenar eminence were also made. See fig. 2.

When the Kipp microgalvanometers were used, pulsatile variations in arterial temperature of  $0.1^{\circ}$  to  $0.15^{\circ}$  were often visible in both the brachial and radial arteries, if the environment was cold. Even the dicrotic waves could sometimes be recognized in spite of the relatively slow characteristics of the galvanometer. Such pulsations could not be ascribed to loss of heat from the vessel to the air along the needle, for they were later confirmed with the other type of couple, in which thermal conductivity was negligible.

#### *Observations with plastic-covered couples*

The first experiment of this series (*exp. 11*) to be considered was carried out in a very warm room. It is selected because in this experiment the thermocouples were inserted considerable distances for the purposes of x-ray demonstration; there can therefore be no doubt of their presence in blood vessels. A tendency to bleeding along the tract, as well as the high initial

temperatures, guaranteed that the 'arterial' thermocouples were within the arteries rather than in venae comites. Figure 1 reproduces x-ray photographs showing the couples within the vessels of the upper arm and forearm.

*Abbreviated Protocol. Experiment 11.* Room temperature  $33.9^{\circ}\text{C}$ . dry bulb and  $28.3^{\circ}$  wet bulb. Thermocouples were introduced in the following order: 1 in rectum to depth of about 15 to 20 cm.; 2 in left femoral artery with insertion to depth of over 15

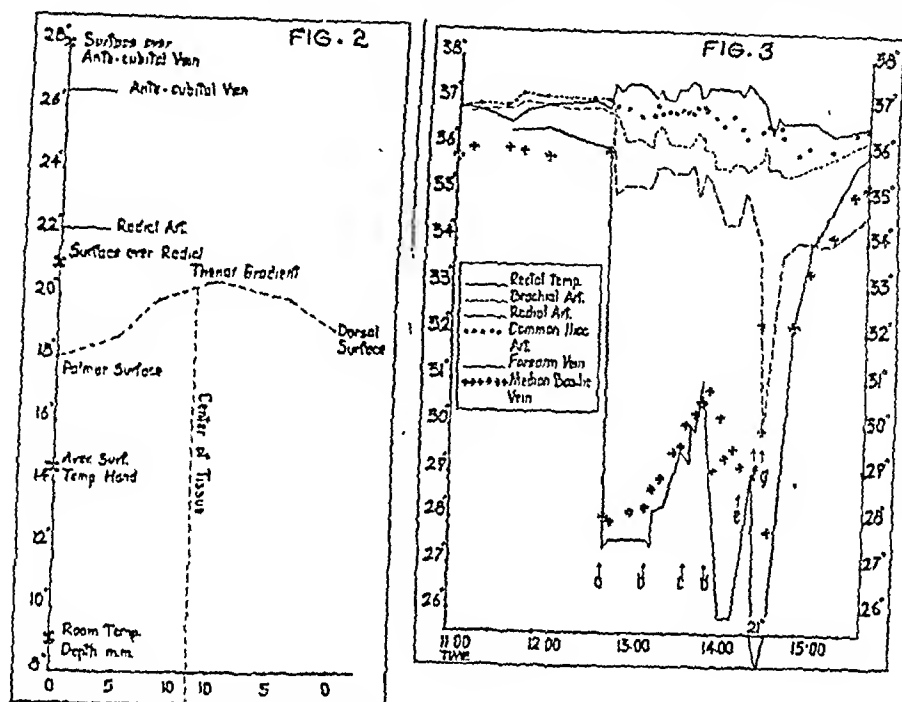


Fig. 2. DATA FROM EXPERIMENT 4 approximately corrected to represent conditions at the time of the second puncture of the radial artery. The abscissae represent the depth in mm. from the puncture on the palmar surface of the thenar eminence to the center of the tissues, and to the exit of the needle (zero depth to the right) on the dorsal surface of the space between the 1st and 2nd metacarpals. The ordinates represent temperatures in  $^{\circ}\text{C}$ .

Fig. 3 (*Exp. 11*). TIMES IN HOURS OF THE DAY are plotted as abscissae and the observed temperatures as ordinates. The upper continuous line indicates the rectal temperature, recorded from the most central locality on an anatomical basis. The lower continuous line indicates the temperatures of the forearm vein, which was the most peripheral couple. The temperatures observed in the brachial artery (middle of upper arm) and in the radial (middle of forearm) are shown by the upper and lower dotted lines. The solid circles indicate temperatures recorded in the common iliac artery and the crosses those in the median basilic vein. At point *a* the left arm was inserted somewhat obliquely to the middle of the forearm in water at  $19.3^{\circ}\text{C}$ ., but the thermocouples in the forearm remained slightly above the level of the water. The temperature of the water rose steadily to  $27^{\circ}$  within the next 72 minutes to the time marked *c*. At point *b* both feet were immersed to some 6 inches above the ankle in water at  $18.8^{\circ}\text{C}$ .; the temperature of this water gradually rose to  $22.4^{\circ}$  at point *c*, when it was lowered to  $13.5^{\circ}$  by the addition of ice. At point *d* the temperature of both baths was lowered further by ice to levels of  $7^{\circ}$  to  $8^{\circ}\text{C}$ . The cooling was rapid enough to cause considerable pain both in the arm and feet, so that the arm had to be removed temporarily from the water shortly after *d*; the arm was returned to the water at *f* while the feet were removed; at *g* the arm was also taken out, and both arm and feet thereafter remained in the air in the warm room. There was some tendency to faint, accompanied by a cold sweat in the period between *e* and *g*. Normal sweating from heat had ceased about 13:40 and returned at 14:50. The temperature in the wrist vein fell at 14:30 to  $20.3^{\circ}$ , at 14:33 to  $20.1^{\circ}$  and at 14:36 to  $21.5^{\circ}$ , as is approximately indicated in the insert below the abscissa line.

cm. so that the couple must have been in the *common iliac*; 3 in left *brachial artery* inserted about 15 cm. to a level 12 cm. above the elbow joint in the middle of the upper arm; 4 in left *radial artery* inserted to a distance of about 15 cm. above wrist joint to the middle of the forearm; 5 in left *median basilic vein* inserted to a level equivalent to that of the brachial couple; and 6 in the *superficial vein draining the left index finger*, punctured in the neighborhood of the anatomical snuff box just distal to the wrist joint with the couple inserted for about 12 cm. to the middle of the forearm. For positions of 3, 4, 5 and 6 see figure 1.

The position of all the couples with the exception of 6 was definite. Thus the venous couple 5 passed up the superficial vein and could be palpated just beneath the skin in the middle of the inner aspect of the upper arm. However, the thermocouple 6 introduced into the tributary of the same vein at the wrist could not be so palpated, even though according to the x-rays (which were taken in two planes) it passed up the forearm along the path of this superficial vein. Possibly the somewhat thick wall of the vein merely prevented its recognition. The distance between the two couples in the arm arteries was estimated as 21 cm. and that between those in the veins as 25.5 cm. The rectal thermocouple was introduced at 9:45 a.m. and couple 6 was introduced at 11:35.

The temperatures recorded during this experiment are shown in figure 3 from 11:00 till 15:45, and the procedures followed are indicated in the subscription of this figure.

In the warm room the subject was sweating until loss of heat to the cooled limbs caused its cessation slightly before the point *c* indicated in figure 3. During the initial period the temperatures recorded in the rectum and in the vessels did not differ greatly. Either the rectum, common iliac or brachial artery might temporarily show the highest temperature, and the temperature of the radial could also exceed for a while that of the rectum. The differences were small. The venous temperatures were not much lower. In the warm environment the temperature of the more central median basilic vein was below that of the wrist vein (cooling of blood in its return passage), though this reversed venous gradient disappeared when the hand was cooled. These differences in the venous thermal gradients are typical of warm and cold conditions. When the hands and feet were cooled in water (at *a*, *b*, *c*, and *d* in fig. 3) considerable discrepancies were observed between the rectal temperature and those recorded in the arteries. The arterial temperatures also differed among themselves. Large gradients were set up between the brachial and radial. The initial effect of cold applied to the peripheral part of a limb was usually to produce rises in temperature in the rectum and central arteries, which, however, were temporary. During rewarming, the temperatures in peripheral vessels started to rise while those of central vessels were still falling. When limbs were put in or out of cold water, at the late stages of this experiment, conditions were complex.

The marked cooling of a central large artery, that may result ultimately from exposure of a more peripheral area to extreme cold in the presence of vasoconstriction (as the result of a cool environment), is well illustrated by



*experiment 12.* The temperatures recorded in this early experiment were obtained with a single plastic-covered couple introduced first into the radial artery and then later into the brachial where it was retained for 135 minutes. Surface temperatures were also recorded from the area over the brachial couple.

*Abbreviated Protocol Experiment 12.* Room temperature  $13.3^{\circ}$  dry bulb, relative humidity moderate. The subject entered the room at 14:30 with a rectal temperature of  $37.5^{\circ}\text{C}$ . After exposure of the subject in shirt and light trousers for 25 minutes the radial temperature was  $33.0^{\circ}$ . At 15:06 the brachial was punctured and the thermocouple was introduced centripetally along it. When introduced a distance of about 2 cm. along the artery a temperature of  $35.1^{\circ}$  was recorded; there was some bleeding along the track of the needle and light compression below the position of the couple was being used. On cessation of this bleeding the compression was removed and the temperature fell to  $34.4^{\circ}$  and only rose another  $0.1^{\circ}$  on introduction of the couple to a distance of 4.5 cm. The needle was then removed causing a return of bleeding, to control which compression of the artery was employed at the point of puncture distal to the couple. During this compression the arterial temperature rose to  $36.1^{\circ}$ , and later fell again to  $35.25^{\circ}$  after removal of the compression. Manual compression of the brachial artery above the level of the couple on the other hand caused only slight falls in temperature (of about  $0.2^{\circ}\text{C}$ . in 15 seconds) with a return to a value slightly above that originally recorded soon after the compression was released. After this the subject sat quietly in the cold room for 20 minutes during which time the brachial arterial temperature fell slowly from  $34.7^{\circ}$  to  $34.0^{\circ}$  while the skin temperature superficial to it varied between  $22.1^{\circ}$ ,  $21.8^{\circ}$  and  $22.5^{\circ}$ . At this time the subject had been sitting for 100 minutes in the cold room. At 16:10 ice water was sponged over the hand and forearm but all applications were at least 15 cm. distal to the position of the couple. The temperature in the brachial artery began to rise within 10 seconds, increased  $0.6^{\circ}$  in 1 minute and  $0.86^{\circ}$  in  $3\frac{1}{2}$  minutes after which it began to fall again slowly. The surface temperature over it also rose  $0.4^{\circ}$ . After the peripheral sponging had been continued for 10 minutes the surface temperature over the artery had fallen by  $0.6^{\circ}$  to  $21.9^{\circ}$  but the brachial arterial temperature though falling was still  $0.5^{\circ}$  above its original value. The hand and forearm were then sponged with water at  $20^{\circ}\text{C}$ . This cold water felt by contrast very warm and some flushing of the skin could be seen. The warming of the skin peripherally initiated a cooling of the brachial artery starting within 4 or 5 seconds and caused a fall from  $34.5^{\circ}$  to  $31.6^{\circ}$  in 5 minutes, while the surface temperature over the vessel showed no significant alteration. At this time (16:28) the subject moved to a warm room for x-ray examination and returned to the cool room 35 minutes later. In spite of the long exposure to warmer conditions the skin temperature had only risen by  $0.7^{\circ}$  to  $22.7^{\circ}$  and the brachial artery by  $0.4^{\circ}$  to  $32.0^{\circ}$ . Six minutes after entering the cold room it had risen to  $32.75^{\circ}$ . Ice water was reapplied to the hand and forearm for 10 minutes with a fall of brachial temperature to  $31.1^{\circ}$  without any initial rise. Lastly, 171 minutes after entering the room, the couple was gradually removed by withdrawing it back along the artery (distally). Dislodging the tube started bleeding, which again necessitated manual compression below the couple. The temperature within the artery steadily rose from  $31.1^{\circ}$  to  $33.3^{\circ}$  during this compression even though the couple was being withdrawn through a distance of 4 cm. during this period. Rectal temperature at the conclusion of the experiment was  $36.6^{\circ}$ .

This experiment has been described in some detail since it demonstrates how great may be the cooling imposed on a large artery like the brachial by cooling followed by rewarming applied peripherally. Such a central artery showed an initial rise in response to peripheral cooling and a later precipitous fall, when the peripheral area began to rewarm. These changes are entirely similar to those normally seen in the rectum when the whole body is cooled and then warmed, but they are much more in evidence in vessels than in the rectum. Lastly, the experiment shows that during such exposure to cold only slight changes in the arterial temperature are produced by manual compression central to the couple. On the other hand a rapid rise is induced if such manual compression is applied distal to the thermocouple in such a way as to impede the return of blood along the veins adjacent to the artery. The experiment therefore gives additional evidence of exchange of heat between the warm blood in the artery and the cold blood in the veins.

One more experiment may be quoted. It differed from the others in that the subject was exposed at first for a long time to a cold room, and then the room was warmed rapidly and was maintained at the higher temperature, while local warming and cooling were employed on the experimental limb. This experiment employed photographic recording and gave therefore indications of the rapidity of changes. On the other hand the temperature levels were open to doubt probably to the extent of  $1^{\circ}$  to  $1.5^{\circ}\text{C}$ . during the period when the room was being warmed, since the recording equipment was also exposed to the rising temperature and parasitic currents could have been present.

*Abbreviated Protocol. Experiment 13.* Room temperature  $21^{\circ}$  dry bulb and  $15.5^{\circ}$  wet bulb. The subject had been exposed to moderate summer weather and the room felt comfortable. The course of the initial stages of the experiment is indicated in figure 4. The rectal temperature there shown was taken 25 minutes after the room was entered. An initial puncture of the left radial artery caused a partial faint, during which the temperature of  $34.8^{\circ}$  was recorded. After 8 minutes, recovery was not complete, so the couple was withdrawn and introduced on the right side 25 minutes later without trouble. Couples were then inserted into other vessels of the right arm as indicated in the figure. The estimated distance each couple passed centrally after entering the vessel was for the arteries 2 cm., for the wrist vein  $5\frac{1}{2}$  and for the median basilic vein 4 cm.

Conditions in the wrist vein were exceptional. The point of introduction was similar to that used on the left arm in *experiment 11*. However, the superficial veins were constricted and the couple passed directly deep to the point of entry along a chance communicating vein to travel up the forearm in deep tissues. It was probably in close apposition to the radial artery. Unfortunately circumstances prevented x-ray examination, but the couple on removal retained a Z shape strongly confirming this interpretation of its position.

The procedure consisted of sitting still till 12:55 in the cool room and then in a rapidly warming room till 14:15 after which the room temperature remained about  $34.5^{\circ}$

dry bulb and  $28.0^{\circ}$  wet bulb. During this time the only experimental modifications of conditions were manual arterial compressions for two minutes each, in the middle of the forearm in the cool room at 10:56, in the rapidly warming room at 13:43 and in the stabilized warm room at 15:45. The first caused a fall of radial temperature of  $1.7^{\circ}$ , the second a fall of  $0.6^{\circ}$  and the last produced no definite change. The temperatures of the wrist vein were recorded simultaneously in the second and third compressions. The second compression gave a fall of  $0.2^{\circ}$  (much less than that of the artery) and the third no significant change. The temperatures recorded at the end of the warm period appeared high, but as has been stated the apparent levels may have been somewhat distorted by parasitic currents. Records were obtained photographically and changes were known accurately. Even at the end of this experimental warm period the close approximation of brachial and radial temperatures recorded in *experiment 11* was not seen.

After 15:50 the effects of hot and cold baths applied to the hand *distal to all the thermocouples* was tested; these observations are shown in figure 5, where the time scale is expanded to make the changes clearer.

The photographic records demonstrated that considerable 'pulsatile' changes in temperature may occur in an artery, particularly during the readjustments to new conditions. Samples of the records are shown in figure 6. It will be noticed that marked pulsations are visible in the records from the arteries in the early stages of cooling in the cold room and again during the recovery after the hand had been violently cooled. In the latter the increased 'pulsation' accompanying a missed beat may be seen, amounting in this case to about  $0.7^{\circ}\text{C}$ . The actual changes must have been greater, since the damping of the thermocouple change by the plastic cover and of the record by the inertia of the galvanometer would both tend to minimize the responses.

The rectal temperatures were taken with an ordinary clinical thermometer at the beginning and end of the experiment. If they had been taken at a deeper level with a thermocouple they might have been somewhat higher but any error is unlikely to have exceeded  $0.3^{\circ}$  to  $0.5^{\circ}$ .

Both in cold and warm rooms the deep vein in the wrist showed higher temperatures than did the more central but more superficial vein, except when the hand was cooled in water. The deep peripheral vein was much more affected by the condition of the hand and its temperature could approximate that of either cold or hot water, to which the hand was exposed. The changes recorded in the temperature of both the radial artery and of this vein seemed to be mutually interdependent. The marked fall of radial temperature on exposure of the hand to very cold water was explicable as a secondary effect of the much greater change observable in the vein.

#### DISCUSSION

The experiments were diverse in character but had one common objective, namely the demonstration of the absence of uniformity or constancy in 'blood temperature'. None of the positions explored can be assumed to indicate with certainty the temperature level or the direction of change of temperature of the thermo-regulating center, for all may be affected by

local conditions. One might expect that the temperature of the abdominal aorta or that of the jugular bulb might be reliable indicators of the temperature of the center. The data here reported, however, indicate that the common iliac artery is not entirely free from the effects of local cooling. Measurements made in the jugular bulb will be reported later, but even in this vessel local influences probably are not negligible. A common central temperature, more or less identical in the main central vessels, is found only

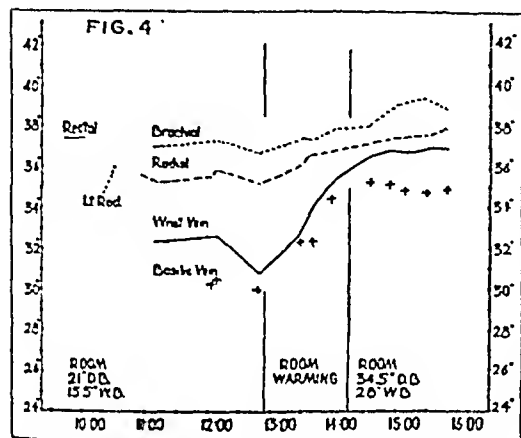


Fig. 4 (Exp. 13). SCALES AND SYMBOLS used follow those of figure 3. Rectal temperature, measured only before and after the experiment, is shown at the start of this figure and at the end of figure 5. The room was entered at 9:25. The room temperature was raised after 12:55 and attained a new steady level at 14:15, at which time the subject had already begun to sweat.

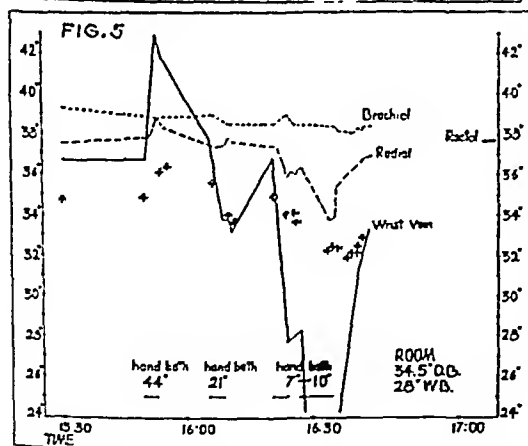


Fig. 5 (Exp. 13). THE LATER PART OF THIS EXPERIMENT IS SHOWN. The hand to the level of the wrist (below the thermocouples) was immersed in hot or cold water as indicated. The time scale has been enlarged as compared with figure 4 to make the relations more evident.

when an individual has been maintained at rest for a considerable interval in a warm room, and when a rapid circulation has aided the attainment of a steady state, as was the case in the early part of *experiment 11*.

The absence of a definite uniform central temperature is perhaps less disturbing than are the very great gradients in temperature that exist in periods of readjustment, not only in the tissues but also in the blood stream along the course of the main arteries. Under such conditions temperature

is a very variable factor, and the process of rewarming may be associated with paradoxical steep falls in temperature in some localities.

There are many indications of a rapid transfer of heat from an artery in its course along a limb under all conditions except those of a warm environment. The existence of a steep thermal gradient across the thin wall of an artery, which as indicated in table 1 may amount to  $1^{\circ}$  or  $2^{\circ}\text{C.}$ , must necessarily be associated with considerable heat transfer. High thermal gradients between brachial and radial arteries, as indicated in the same table, sometimes reached  $0.35^{\circ}/\text{cm.}$  These temperature differences were substantiated by marked pulsatile changes in arterial temperature, which often were obtained. Some of these are reproduced in figure 6. Such variations in temperature with the pulse were particularly marked in periods of readjustment when thermal conditions were rapidly changing.

Rapid cooling of blood within an artery, as indicated by all these observations, cannot occur unless the heat is accepted by some other tissue, yet warmer skin surfaces lying over arteries were not observed. An exchange of heat between the arteries and adjacent venae comites, by which the returning blood is warmed as the arterial blood is cooled, provides the only reasonable explanation. Under such conditions pulsatile rewarming of venous blood should also occur. Some indication of such a phenomenon has been obtained, but any evidence was inconclusive. Only lack of imagination has prevented scientists from realizing how great must be the exchange of heat between such vessels at different temperatures separated by thin walls with little capacity for insulation. The anatomical conditions in a peripheral artery such as the radial are evident in a diagram utilized by Leonard Hill *et al.* in 1897 (8) for another purpose. It would be difficult to imagine any anatomical arrangement more suited to heat exchange.

The effects of vasomotor changes on such a system cannot be simple. The known factors may be considered by taking as an example the vasodilatation to warmth following exposure to cold. Increased rapidity of flow shortens the duration of exposure of arterial blood to cooling effects, and tends to decrease the degree of cooling. On the other hand the increased rapidity of flow in the veins decreases the rewarming of venous blood and so extends centrally the distribution of cooled venous blood. Thus the thermal gradient between the vessels temporarily is increased counteracting any tendency to reduced heat exchange per ml., and accounting for greater pulsatile changes in temperature.

The interaction of these various factors gives complicated effects during rewarming. Commonly the vasodilatation causes an initial rapid return of cooled venous blood, which through its low temperature and large volume

accepts much heat from the artery and induces a rapid fall in temperature in peripheral arteries. The rapidity of blood flow later reduces the thermal difference between the artery and the periphery (i.e., raises surface temperature). The temperature at which the venous blood starts its return passage is increased, as is that of the blood in the main venous channels. Consequently, the ultimate effect is a general increase in temperature in all these vessels including the artery.

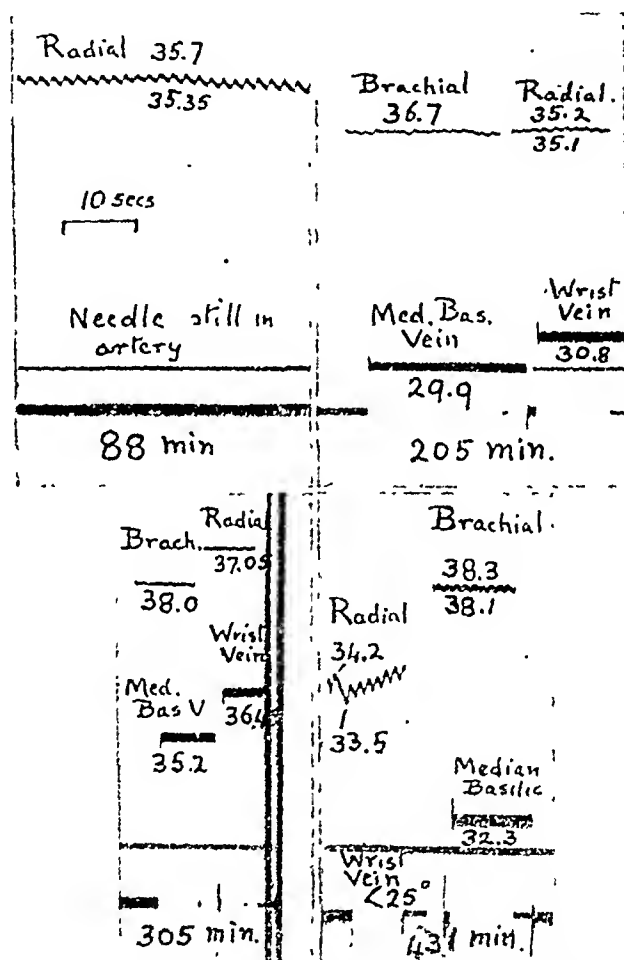


Fig. 6 (Exp. 13). REPRODUCTIONS OF ACTUAL RECORDS *top left*, from the radial artery at 10:53 after subject had been exposed to the cool room for 88 minutes. The needle, through which the couple had been introduced, was still in the artery but distal to the couple. *Top right*, records from arteries and veins at 12:50 just before the room was warmed. The subject was in approximate equilibrium after 205 minutes in the room. *Bottom left*, similar records obtained at 14:30 when the warm temperature of the room had been steady for 15 minutes. *Bottom right*, records obtained at 14:36 just after removal of the hand from very cold water and 431 minutes after the subject entered the room.

When the dilatation follows a period of exposure to cold, the sudden increased thermal conductivity also affects the situation through the more rapid convective transfer of heat. The tissue insulation values are reduced and the peripheral areas of the body are heated at the expense of those more centrally located. The rapid fall in the temperature of the brachial artery, such as that observed in *experiment 12* must be regarded as such a reaction and one entirely comparable to the fall in rectal temperature that accompanies the initial stages of rewarming after the whole body has been cooled.

The rise in arterial temperature in the response of vasoconstriction such as occurred in *experiment 12* is an example of the opposite reaction. The temperature of the returning venous blood is lowered but its rate of flow is also slowed. The artery is at first exposed to a smaller quantity of blood cooled to the normal extent and its temperature rises. Later the colder venous blood reaches central positions and the arterial temperature falls. When the venous blood has not been originally greatly cooled, the rise resulting from slowed flow may not be seen, as was the case in *experiment 11* at point *a*. Where the cold stimulus is extreme, and where preceding alternations of vasoconstriction and dilatation complicate the picture, the initial increase in temperature in the central arteries also may be absent, as was the case at the end of *experiment 11*.

Conditions in the rectum are those of an area, which is centrally located but which is supplied with blood affected by local cooling or warming. Both the arteries and veins of the rectum anastomose freely with those supplying neighboring skin, such as that of the buttocks. The common iliac artery is demonstrated not to be immune from cooling effects arising in the iliac veins, so that the inflow of blood from the internal iliac artery must also be affected by venous return in these vessels. Thus cooling of such vessels from local exposure of the legs could exert cooling effects on the rectum greater than those to the body as a whole. In addition venous blood from the buttocks has a possible path for return through the connections with the rectal vessels. The use of this path may perhaps be affected not only by vasomotor reactions but also by postural changes. Any return along such paths would be apt to affect the temperature of the arterial inflow, and reduction of such venous flow by vasoconstriction would be the most likely explanation for the sudden rise of rectal temperature that accompanied the immersion of a single arm in cool water in *experiment 13*.

None of the vessels investigated is representative of central body temperature for they all appear to be affected by local temperature changes. Thus in *experiment 11*, after immersion of the hands in cold water, discrepancies between rectal and arterial temperatures reached values of  $0.5^{\circ}$ ,  $1^{\circ}$  and  $2^{\circ}\text{C}.$ , respectively, for the common iliac, brachial and radial, while later

immersion of the feet in cold water gave different relations. The greatest cooling in the central areas in this experiment occurred in the period of re-warming when all the limbs had been removed from the bath, but they developed with very different degrees of lag. The minimum developed in the median basilic vein after some 5 minutes, in the brachial and femoral after 15 minutes and in the rectum after 45 minutes. The cooling of the central vessels and rectum in this experiment had to have a peripheral origin since the room was very warm. The temperature of the radial artery fell below room temperature, though the point of measurement was well above the water level, while even the brachial temperature fell to a value only  $1.7^{\circ}$  above that of the room with an abruptness incompatible with mere air-cooling.

Precooling of arterial blood by venous blood would appear teleologically to be a disadvantage in the adjustment of an individual to a warm environment. However, under such conditions the superficial veins are dilated and venous return is mainly through low resistance superficial paths, along which cooling can continue. Possibly some reciprocal constriction of deep veins occurs, but no method of investigation has been found. The superficial venous return, however, can account for reversed surface thermal gradients in the forearm in the warmth described by Pennes (9), for the high temperatures of finger and toes (5, 10) as well as for reversed thermal gradients in the superficial veins here reported and also earlier described (4).

Bizarre effects may be seen. Thus in *experiment 11* during recovery the radial artery temporarily appeared to have a temperature lower than that in a superficial vein. Whether true or not, such a condition is not impossible. An effect, in which cooled arterial blood rapidly lowered the surface temperature of a hand during re-warming, is described as another instance in a later paper (11).

The statement has been made (12) that exposure of the skin surface to cold causes an initial but temporary rise in temperature within the neighboring muscle and that this indicates a vasodilatation in the blood vessels to the muscle in the response to cold. The observations are undoubtedly correct, but the deductions are not warranted in view of the data here reported. The change in muscle temperature merely parallels that which long has been known to arise in the rectum, and which is described here in the large arteries. The change could occur merely as the result of a reduced return of cooled venous blood due to constriction of skin vessels and a consequent rise in temperature of the blood supplying the muscle. There is, however, no definite evidence that dilatation might not occur also; this point remains an open question.



The values here given for arterial temperature are not in disagreement with those in the literature; they merely were obtained under a much wider range of conditions and so have demonstrated the existence of larger variations. Previous values given by Bazett and McGlone (4) agree with them, though these earlier values were cited with some diffidence. Pennes (9) has reported in warm rooms temperatures in brachial arteries which agree with those obtained here under similar conditions.

The variety of temperatures recorded in the large vessels and the differences that may exist between the temperature of the rectum and temperatures in the large central vessels render past evidence on temperature control open to doubt. Reexamination of this subject has already started and the data obtained will be reported later.

In conclusion it is pertinent to remark on the misconceptions that arise from the fictitious assumption of a uniform 'body' temperature. Not only is tissue temperature variable even in homoiotherms, but important variations in arterial blood temperature are common. Thus the blood in arteries such as the radial artery and dorsalis pedis may have a temperature between 20° and 25°C. Such temperatures imply an increase in resistance to flow, from the change in blood viscosity alone, of some 30 per cent, even supposing that the increase in viscosity of the blood in the vessels is no greater than that which would occur in water. It is certainly unlikely to be less than this. On the contrary in still smaller vessels, such as the digital arteries, both the temperature change and that in viscosity are likely to be much greater. The physiological and medical significance of such changes may be great.

Other effects of temperature changes must also be present. Cooling alters the dissociation of water and the pH at neutrality; isoelectric points of proteins are altered and the blood becomes much more alkaline (13-15), while the dissociation curves of blood for gases are shifted, altering the actual gas tensions in the tissues (16). Temperature changes alter the balance of electrolytes in the blood between corpuscles and plasma (17). It is possible that chemical or osmotic differences set up by thermal gradients are concerned in the stimulation of thermo-receptors (18). All these changes indicate an urgent need for the study of temperature as a variable in the biochemistry and physiology of blood and tissues.

#### SUMMARY

1. Measurements of temperature in the brachial and radial arteries and common iliac artery as well as in superficial veins are reported. Thermo-couples were left in place for hours and the effects of cooling and heating on vascular temperatures were determined.

2. The temperature of the blood in transit in the limbs, even in the arteries, is by no means either uniform or constant. It varies in different

vessels at any one time, and in any single vessel is much affected by the conditions of cooling distal to it. A gradient of  $0.3^{\circ}\text{C}$ . per cm. or more may exist along the brachial and radial arteries, and pulsatile changes in temperature of  $0.2^{\circ}\text{C}$ . or more may accompany each pulse wave.

3. Cooling of arterial blood in transit in the arteries of the limbs is dependent on the rewarming of cold blood returning in adjacent veins from more distal areas. If the blood in these veins is cold, compression hindering flow causes a rise in temperature in the artery proximal to the point of compression.

4. Temperatures as low as  $21.5^{\circ}\text{C}$ . for the radial and  $31.1^{\circ}$  for the brachial artery have been recorded without the subject's being unduly cold, or the rectal temperature particularly low.

5. The temperatures of the rectum, brachial artery and common iliac artery may all differ considerably from one another and undergo changes of different magnitude and with greatly different degrees of lag.

6. The temperatures in superficial veins of the wrist and forearm are much lower in a cold environment, the more peripheral the point of measurement. In a hot environment this gradient is apt to be reversed.

7. Attention is drawn to the chaos introduced into physiology by the fictitious assumption of a constant blood temperature.

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## Heat Loss and Blood Flow of the Feet Under Hot and Cold Conditions<sup>1</sup>

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**A**LTHOUGH THE IMPORTANCE of the extremities in thermo-regulation is well established little has been done to follow progressive changes in these areas during relatively long exposures to heat and cold. There are available the results of Burton (1) showing a gradual increase in finger blood flow during several days of exposure to heat and a gradual decrease during exposure to cold. In this same paper it is shown that the superficial veins of the forearm become fully dilated in the heat and fully constricted in the cold only after some time. There are also observations on the amount of convective and radiant heat loss from the hand which show that the proportion of heat lost by the different pathways can change during the course of exposure (2).

The experiments to be reported here were designed to extend these relatively long-range observations. Measurements were limited to the foot and included the evaporative and non-evaporative heat loss, blood flow and skin temperature of subjects living in a controlled temperature room for periods up to two weeks. Except for several short experiments done to confirm part of the results the same two subjects were used throughout. Only two room conditions (approximately 33°C. and 21°C.) were used and the subjects were exposed to both of these temperatures during the summer and again during the winter.

Blood flow measurements were made by the venous occlusion technique. The heat exchange of the foot was obtained by the use of a calorimeter similar to that described by Forster, Ferris and Day (3) for use on the hand. The two were not combined into one instrument as was done by Forster *et al.* but the calorimetric measurements were made on one foot, while the plethysmograph was used on the other. 'Such an arrangement has the disadvantage that the two feet were not subjected to the same conditions due to the sup-

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pression of vaporization and the absence of air movement in the plethysmograph. In spite of this, the arrangement used was preferred because otherwise blood flow measurements could not have been interspersed at will with calorimetric determinations. Stopping the air movement in the calorimeter to measure blood flow would cause a rise of temperature of such extent that further calorimetric determinations could be made only after the air circulation had been restored for some time. In view of the large variation in blood flow during any one day many observations were necessary. It was thought best to obtain these simultaneously with the calorimetric data even though it necessitated exposing the two feet to different conditions.

#### DETAILS OF CONSTRUCTION AND USE OF THE APPARATUS

*The Calorimeter.* This was a double-walled copper vessel (capacity, 7.5 liters) shaped like a boot. Air entered through two openings at the level of the toes and left by a single opening at the back of the ankle. The volume rate of air flow was 50 liters/minute. The estimated linear air velocity was 2 to 3 meters/minute. The effective air movement was probably greater due to turbulence. The foot was sealed into the calorimeter and cork stops kept it from touching the metal wall.

The calorimeter was suspended in air on a framework. The air movement in the room was constant and was estimated at about 35 meters/minute. Standardization was accomplished with an electrically heated coil fitted into a boot. The heat loss to the air was measured with a thermocouple of high sensitivity with one junction in the inlet air stream and one in the outlet. A similar thermocouple was used to measure the thermal gradient across the walls. The constant relating this gradient to the heat loss across the walls was determined empirically. A series of measurements over a period of a year with different room conditions gave estimates of the heat recovered which ranged from 99 to 104 per cent of the heat input.

Evaporative heat loss was determined gravimetrically. For most purposes the evaporative heat loss has been calculated from the mass of water lost using the constant for the heat of vaporization at the average surface temperature of the skin. For more exact purposes allowance must be made for the expansion of the water vapor to the volume corresponding to the relative humidity attained in the calorimeter, as has been emphasized by Murlin and Burton (4) and Hardy and DuBois (5). Calculations of this type have been made on the data only in comparisons of the insulating value of air at different temperatures to make certain that apparent differences were not due to such factors.

In making these corrections the cooling of water vapor from the temperature of the skin to that of the calorimeter has been considered negligible. The expansion of the water vapor is not negligible, since the relative humidity of the calorimeter was estimated sometimes to be as low as one per cent, but the amount of heat absorbed by the gas in this expansion cannot be calculated with certainty. The maximal amount of heat that could be absorbed is that involved if the process took place very slowly against an external pressure which at all times was only infinitesimally less than the gas pressure (i.e., in a thermodynamically reversible isothermal expansion). In this case the heat absorbed would be equal to  $p/v$  or  $RT \ln p_1/p_2$ . The minimal heat absorbed is that involved on

the assumption that the expansion of the gas takes place against a pressure at all times equal to the final pressure. In this case the heat absorbed is equal to  $p\Delta V$ . At very low humidities there is considerable difference between the heats calculated in these two ways. For example, if the relative humidity of the calorimeter was one per cent and the temperature  $27^{\circ}\text{C}$ ., the upper limit is 0.153 Cal/gram and the lower limit 0.033 Cal/gram. No information is available to determine what value should be used between these limits, so that both corrections have been calculated, whenever the correction has been applied.

*The Plethysmograph.* The plethysmograph was a copper vessel of 3.5 liters capacity shaped roughly like a boot. The plethysmograph and calorimeter were the same height. It was air filled and air transmission was used throughout. Optical records from a Frank capsule were obtained on paper moving at 1.7 cm/second. Calibrations were made after each experiment by introducing measured amounts of water. This was done with the foot in place and the circulation occluded. The excursion was linearly related to the amount of water introduced ( $\pm$  about 5 per cent) and there was no overshoot unless the water was introduced at a rate in excess of the largest blood flows.

No water bath was used since it was found that changes in the base line were so slow as to be insignificant in the few seconds required for a measurement.

The occlusion pressure was 100 mm. Hg. A similar pressure was found to be necessary for the dependent foot by Abramson *et al.* (6). The apparent venous pressure was regularly found to be 30 to 40 mm. Hg. The artefact produced by inflating the cuff was recorded. Its maximum duration was determined by the method of Wright and Phelps (7) to be one second. The blood flow was measured from the first pulse after the end of the artefact time, for, as has been found by Wright and Phelps (7) and Christensen and Nielsen (8), the pressure rise after venous occlusion is often not linear.

*Skin Temperature Measurements and their Probable Accuracy.* Skin temperatures were obtained with 36-gauge copper-constantan thermocouples of low sensitivity which could be read to  $\pm 0.1^{\circ}\text{C}$ . They were attached to a single Kipp and Zonen galvanometer through a selector switch. Recording was photographic. They were held to the skin with adhesive or Scotch tape. Four were used on each foot. The locations were as follows: 1) dorsal surface of the middle phalanx of the middle toe; 2) the center of the sole; 3) the Tendo-Achilles at the back of the ankle; and 4) the outside of the ankle just below the external malleolus. These positions were selected as a result of experiments in which the foot was divided into eight transverse segments with two thermocouples in each segment. The arithmetical mean of the four points designated was found to agree closely with the average skin temperature determined with the 16 thermocouples under conditions in which the temperatures covered a range between  $17.6^{\circ}\text{C}$ . for the toe and  $26.5^{\circ}\text{C}$ . for the back of the ankle (9).

In some later experiments the skin temperature was measured with a 130-cm. length of 38-gauge Hytemco wire which was used as a resistance thermometer. It was wrapped in two loops parallel to the long axis of the foot and cemented to the skin with a band of cement which was not more than 5 mm. wide. This arrangement should give a better average surface temperature since evaporation was suppressed in only a narrow zone over which a large thermal gradient was less likely than with the thermocouple coverings. A series of simultaneous measurements was made by the two methods. In the cold the resistance thermometer gave values which averaged  $0.8^{\circ}\text{C}$ . below the thermocouple values. In the heat this difference increased to  $1.3^{\circ}\text{C}$ .

*Routine of the Experiments.* The characteristics of the two subjects are given below.

	Subject R	Subject Y
Age	23	21 years
Height	178	160 cm.
Weight	59.0	51.1 kgm.
Surface area (DuBois formula)	1.74	1.51 m <sup>2</sup>
Average foot volume in heat	1400	1200 cc
Average foot volume in cold	1300	1100 cc
Average foot area (10)	0.082	0.075 m <sup>2</sup>

Throughout the experiments the subjects wore shorts, undershirt and sandals

Each day began at about 7 a. m. At approximately 8:30 a.m., after a basal metabolism test, the first subject moved to a nearby chair in which he sat while measurements were made on his feet. Preparation of the subject took about 45 minutes. An additional 30 minutes elapsed before records were made. Twenty or more records of blood flow and about 10 observations of temperatures were made during the next period of about 100 minutes. The morning experiment ended about 10:30 and was followed by breakfast. A light lunch was served at 1:00 p.m. and shortly after this the experiment was repeated on the second subject. Subjects were alternated so that a fasting determination was made on each subject every other day.

Variations in the room temperature during the hours of a single experiment amounted to less than 1°C. except on the afternoon of July 21 when a breakdown of the air-conditioning unit occurred.

## RESULTS

The blood volume data from these experiments have been given by Speakman *et al.* (11). Increased values were found under warm conditions. There were three periods of heat (17 days) which allow valid comparisons of the averages of the different periods. Any differences in these averages can be interpreted as evidence of acclimatization to heat which would be expected to be greatest during the first exposure in the summer and least during the winter. Two periods (8 days) were spent in the cold but since the second exposure lasted only 2 days no valid comparisons between the periods can be made. The values obtained in the cold will be used only to contrast the levels found in the heat.

Daily average values are given in table 1 and in figure 1. Average values for entire periods are compared in table 2.

Fluctuations in blood flow during any one day were large in the heat (commonly amounting to changes of 100 per cent) but were small in the cold. Variations in the other measurements were small and no trends were found to indicate that insufficient time was allowed for steady conditions to be reached.

*Levels of Heat Exchange in the Heat and Cold.* The measured basal metabolism was 36 to 42 Cal/m<sup>2</sup>/hr. under both conditions and 45

Cal/m<sup>2</sup>/hr. has been assumed as the probable metabolic level when the subject sat up in the fasting morning experiments. The area within the calorimeter was about 5 per cent of the total body surface and lost 56 Cal/m<sup>2</sup>/hr. in the warmth and 29 in the cold. This implies that this area lost 6.5 per cent of the total heat in the hot condition and 3.5 per cent in the cold. Of the heat lost from the foot 51 per cent was evaporative loss in the

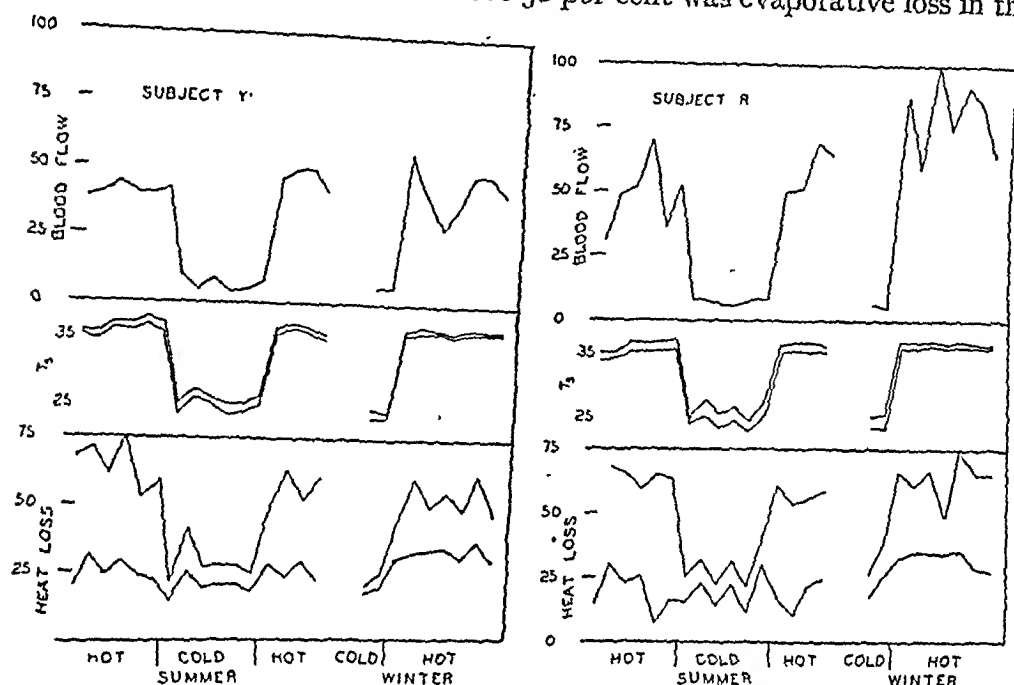


Fig. 1. DAILY AVERAGE VALUES for subjects Y and R. Time of year and condition of the room are indicated at the bottom. Uppermost curve represents blood flow in cc/min., the middle two curves the mean surface temperatures of the feet (the warmer being that in the plethysmograph) in °C., and the lower total and non-evaporative heat loss in Cal/m<sup>2</sup>/hr.

heat and 27 per cent in the cold. Since the subjects were weighed at regular intervals and a complete balance sheet of ingesta and excreta was kept, comparisons of water loss may be made with that from the body as a whole (see table 3). In both heat and cold the water loss from the foot often equalled in intensity that from the body. Non-evaporative heat losses can be compared less accurately on the basis of the assumed heat production. In the heat non-evaporative loss from the body could have been at most 15 Cal/m<sup>2</sup>/hr., while that of the foot was 27. In the cold non-evaporative loss from the body must have been at least 35 Cal/m<sup>2</sup>/hr. while that of the foot was 22.

Blood flow in the heat was 54 cc/min.; it fell to 7 in the cold. Each cc. of blood lost 1 to 2 calories in the heat and 4 to 7 in the cold. Since the warmer foot was in the plethysmograph, the flow of the other foot may have been somewhat less, and the heat loss per unit volume of blood may be somewhat underestimated.

The temperature distribution on the foot differed in the two conditions. In the cold the toe had the lowest temperature. In the heat the gradient was reversed and the toe became the warmest point at a level about 0.5°C. above the average.

Non-evaporative heat losses of all types may be grouped for rough purposes and the thermal insulation value of air be calculated from the ratio of the temperature difference to heat transfer. Such values, expressed in Clo units (12), are shown in table 2 and indicate striking differences between the hot and cold conditions. The levels in the summer and winter differ somewhat (possibly because of slight differences in the room conditions since the relationship of air and wall temperatures was certainly different) but the

TABLE 1. AVERAGE VALUES FOR EACH DAY<sup>1</sup>

DATE	ROOM D.B.	ROOM W.B.	FLTH. FOOT TEMP.	BLOOD FLOW	CALOR. FOOT TEMP.	CALOR. TOE TEMP.	TOTAL HEAT	NON-EVAP. HEAT	EVAP. HEAT	HEAT LOSS OF BLOOD	AIR INSUL.
<i>Subject Y</i>											
1 <sup>1</sup>	32.8	27.8	35.3	38	35.8	34.5	67	21	69	2.3	0.63
2	31.7	28.0	35.6	40	34.1	33.8	72	32	56	2.3	0.28
3 <sup>2</sup>	33.1	28.6	36.9	44	36.1	36.9	61	24	61	1.8	0.53
4	33.3	28.6	36.8	40	35.6	36.2	76	29	62	2.4	0.31
5 <sup>2</sup>	33.1	28.6	37.7	40	36.5	37.0	52	23	56	1.7	0.67
6	33.3	28.0	36.7	42	35.6	36.0	58	22	62	1.8	0.42
7 <sup>2</sup>	20.3	14.9	25.1	8	23.5	21.9	24	15	38	3.8	1.05
8	21.1	14.5	26.9	5	25.9	23.4	37	26	30	9.6	—
9 <sup>2</sup>	20.8	15.7	25.8	7	25.1	22.7	28	20	29	5.1	1.08
10	20.8	16.3	24.8	4	23.3	21.3	29	21	28	9.3	0.49
11 <sup>2</sup>	20.3	15.8	24.9	5	24.1	22.2	28	21	25	7.2	0.82
12	20.3	15.3	26.1	8	24.8	23.1	25	18	28	4.0	1.24
13 <sup>2</sup>	32.2	27.5	36.4	47	35.5	36.2	50	28	44	1.3	0.49
14	33.6	26.4	37.0	50	36.2	36.2	63	24	62	1.6	0.44
15 <sup>2</sup>	32.2	28.3	36.5	50	35.7	35.9	53	30	44	1.4	0.51
16	32.8	28.0	36.4	52	34.9	35.3	61	23	62	1.6	0.36
1 <sup>2</sup>	20.6	15.0	24.4	7	23.1	23.2	23	19	17	3.7	0.60
2			24.1	7	23.3	21.5	26	20	23	5.1	0.57
3 <sup>2</sup>	33.3	28.3	36.2	57	35.7	35.5	44	31	30	1.0	0.28
4			36.8	39	36.0	36.0	61	34	44	1.9	0.29
5 <sup>2</sup>			36.6	29	36.2	36.0	51	35	31	2.1	0.32
6			36.0	37	35.5	36.6	56	36	36	1.9	0.19
7 <sup>2</sup>			36.6	48	36.0	37.3	49	31	37	1.3	0.34
8			36.4	48	36.3	36.9	62	37	40	1.5	0.31
9 <sup>2</sup>			35.4	43	36.1	36.5	47	31	34	1.3	0.35



TABLE I—Continued

DATE.	ROOM D.B.	ROOM W.B.	PLETH. FOOT TEMP.	BLOOD FLOW	CALOR. FOOT TEMP.	CALOR. TOE TEMP.	TOTAL HEAT	NON-EVAP. HEAT	EVAP. HEAT	HEAT LOSS OF BLOOD	AIR INSUL.
<i>Subject R</i>											
	°C.	°C.	°C.	cc/min.	°C.	°C.	Cal/m <sup>2</sup> /hr.	% of total	cal/cc.	Clo.	
1	32.8	27.8	34.9	32	33.7	33.3	—	15	—	—	
2 <sup>2</sup>	32.2	28.0	35.0	49	34.2	34.3	67	30	55	2.0	0.19
3	33.3	28.6	36.6	53	35.3	36.4	66	23	65	1.7	0.20
4 <sup>2</sup>	33.3	28.6	35.5	69	35.3	35.9	60	26	57	1.3	0.34
5	33.3	28.6	—	36	—	—	65	8	88	2.5	0.26
6 <sup>2</sup>	32.8	28.0	36.9	54	35.5	36.2	63	17	73	1.6	—
7	20.5	14.9	25.0	8	23.9	22.1	27	17	37	4.5	0.70
8 <sup>2</sup>	20.5	14.5	27.4	7	25.0	22.6	32	23	28	6.4	0.95
9	20.5	15.7	25.4	6	23.2	22.0	23	14	38	5.5	0.91
10 <sup>2</sup>	20.5	16.3	26.5	6	24.4	22.2	31	22	29	7.7	0.91
11	20.3	15.8	24.4	8	22.8	21.6	21	12	43	3.6	0.81
12 <sup>2</sup>	20.3	15.3	27.8	8	25.2	23.4	39	30	23	6.9	0.99
13	33.3	27.5	36.3	51	35.3	36.0	61	18	71	1.7	0.76
14 <sup>2</sup>	33.9	26.4	36.8	53	35.4	36.2	54	11	80	1.5	0.47
15	33.3	28.3	36.7	69	35.2	35.5	55	22	60	1.1	0.62
16 <sup>2</sup>	32.3	28.0	36.2	65	35.3	35.2	58	25	57	1.3	0.33
1	20.6	15.0	24.9	6	23.4	22.0	27	18	33	5.7	0.52
2 <sup>2</sup>			25.4	5	23.2	21.2	38	26	32	9.6	0.27
3	33.3	28.3	36.8	87	35.8	35.7	66	32	52	1.0	0.25
4 <sup>2</sup>			36.8	60	35.9	35.9	62	36	42	1.4	0.33
5			36.9	99	36.4	37.4	67	35	48	0.9	0.26
6 <sup>2</sup>			36.4	74	35.9	36.8	47	34	28	0.8	0.28
7			36.9	92	36.1	37.4	74	36	51	1.0	0.37
8 <sup>2</sup>			36.5	85	36.0	36.9	67	29	57	1.0	0.37
9			36.3	65	35.8	36.5	66	27	59	1.3	0.37

<sup>1</sup> The first 16 days are those of the summer experiment; the last 9, those of the winter experiment.

<sup>2</sup> Values obtained in the morning with the subject fasting.

ratio of the apparent insulation in the cold to that in the heat is constant (2.1 in the summer and 1.9 in the winter). The validity of this difference will be discussed later.

*Differences Between the Three Periods of Exposure to Heat.* Table 3 shows that the evaporative heat loss of the foot was considerably reduced by previous exposure to cold even when the exposure was as short as the 6-day interval between the two periods of heat in the summer. A similar but smaller reduction can be seen in the 24-hour loss of the whole body. This decreased ability to sweat was accompanied (and probably partially com-

pensated) by a raised skin temperature and an increased rate of non-evaporative heat loss.

Blood flow measurements also show differences between the periods of heat (table 2). In *subject R*, the difference in flow between any two of the three periods of heat was statistically significant, as was the smaller increase shown by *subject Y* for the summer periods. The amount of heat lost by each volume of blood under warm conditions was reduced after exposure to cold; both subjects are consistent in indicating this change.

TABLE 2. AVERAGE VALUES FOR ENTIRE PERIODS

PERIOD	ROOM D. H.	FIFTHS FOOT TEMP.	BLOOD FLOW	COLOR. FOOT TEMP.	TOTAL HEAT	NON- EVAP. HEAT	EVAP. HEAT	EVAP. HEAT	HEAT LOSS OF BLOOD	AIR INSUL.
<i>Subject Y</i>										
	°C.	°C.	cc/min.	°C.	Cal/100/hr.			% of total	cal/cc.	Clo.
Heat I, Summer.	32.9	36.5	41	35.6	64	25	39	61	2.0	0.47
Heat II, Summer . .	32.7	36.6	47	35.6	57	26	31	54	1.6	0.45
Heat, Winter . . .	33.3	36.4	43	36.0	54	34	20	37	1.5	0.30
Cold, Winter . . .	20.6	24.3	7	23.2	25	20	5	20	4.4	0.59
Cold, Summer . . .	20.7	25.6	6	24.5	28	20	8	29	6.0	0.93
<i>Subject R</i>										
Heat I, Summer . .	33.0	36.0	40	34.8	63	20	43	68	1.9	0.34
Heat II, Summer . .	33.2	36.5	60	35.3	57	19	38	67	1.4	0.49
Heat, Winter. . .	33.3	36.7	80	36.0	64	33	31	48	1.1	0.30
Cold, Winter . . .	20.6	25.2	6	23.3	33	22	11	33	6.8	0.56
Cold, Summer . . .	20.4	26.1	7	24.1	29	20	9	31	5.9	0.89

*Evidence of Acclimatization During any One Period.* From the appearance and attitude of the subjects it was apparent that their condition improved during each of the longer exposures but this improvement was not reflected in any of the variables tabulated. The only gradual change which could be demonstrated in the heat was that the toe regularly became the warmest part of the foot. In most of the exposures this rise in toe temperature relative to that of the rest of the foot took several days to develop. In the cold the toe was regularly the coldest of the four points measured with a single exception. This exception occurred on the first morning of one of the exposures to cold.

#### DISCUSSION

The various levels obtained can be compared with the results obtained on the hand by Forster *et al.* (3). The hand experiments in which the sur-

face temperature fell within the limits found for the foot were used for this comparison. In the cold the average blood flow was 1.5 cc/100 cc/min. for the hand and 0.5 for the foot. The flow in the warm foot (5 cc/100 cc/min.) was considerably less than that of the warm hand (16 cc/100 cc/min.). The figures for the heat lost by each volume of blood are in good agreement with the results on the hand, as are the probable temperatures of the blood entering the arteries. These have been estimated (as were those of Forster *et al.*) on the assumption that the blood leaves the foot at a temperature equal to the average surface temperature. It must be concluded that in the heat the arterial blood entered the foot at a temperature only slightly below that of the rectum, while in the cold the incoming blood must have been in the neighborhood of 30°C.

TABLE 3. AVERAGE VALUES FOR EVAPORATIVE WEIGHT LOSS<sup>1</sup>

PERIOD	SUBJECT Y			SUBJECT R		
	Night loss, entire body	24-hr. loss, entire body	Foot loss	Night loss, entire body	24-hr. loss, entire body	Foot loss
Heat I, Summer.....	50	72	63	50	58	75
Heat II, Summer.....	54	66	53	48	55	66
Heat, Winter.....	46	56	34	47	46	54
Cold, Winter.....	5	10	8	10	12	19
Cold, Summer.....	5	11	14	10	12	16

<sup>1</sup> All figures are in grams/m<sup>2</sup>/hr. An approximate correction for the loss of water vapor from the respiratory tract and for the difference in weight of the respiratory gases has been applied to the figures for the body. The correction used was 6 grams/m<sup>2</sup>/hr. in the cold, and 10 grams/m<sup>2</sup>/hr. in the heat.

The total heat loss for the cold foot averaged 28 Cal/m<sup>2</sup>/hr. as compared to 21 for the hand (assumed hand area 0.05 m<sup>2</sup>). Corresponding values in the heat were 55 and 61. However, there is a considerable difference in the amount of heat lost over the various pathways. The foot lost 54 per cent of its heat by vaporization in the heat and 30 per cent in the cold. In contrast to this the evaporative heat loss from the warm hand was 72 per cent of the total and 74 per cent for the cold hand. The probable reason for this difference is that the volume rate of air flow in the hand calorimeter was only one-fifth of that used on the foot. This probably would limit the convective heat loss from the hand more than the evaporative loss and so alter the ratio.

Benedict and Wardlaw (13) have reported that in comfortable conditions the rate of water loss from a unit area of the feet is greater than that for the entire body. In contrast, during profuse sweating the evaporative

loss of the feet was found to be less than that of other areas of the body (14, 15). The figures given in table 3 show that under the conditions of these experiments, in which the foot was exposed to dry air and the rest of the body to moist air, such differences were not apparent.

An essential factor was the reduction of the ability of the foot to sweat in the heat after exposure to cold. This is in accord with the results of Adolph (16) for the entire body. The more marked reduction in the loss from the foot than from the entire body may indicate that the regional differences described by Kuno and Weiner are more marked, or appear at a lower temperature, in the winter than in the summer.

The other differences between the three periods of heat are all probably related to this decreased ability to sweat following an exposure to cold. Thus, the raised skin temperature would result from the decreased evaporative heat loss and would lead to an increased rate of non-evaporative heat loss. The decreased cooling of the blood would result from the decreased temperature gradient from blood to skin. The increase in blood flow, which was conspicuous in one subject and partially present in the other, could be adequately explained as a compensatory mechanism used to keep up the nonevaporative heat loss in spite of the decreased cooling of each volume of blood.

Although no consistent changes in blood flow could be demonstrated during any one exposure to heat or cold, the increase in toe temperature relative to that of the rest of the foot in the heat strongly suggests that the toes have a gradual increase in flow similar to that found by Burton (1) for the finger.

The marked difference in the apparent air insulation for the hot and cold conditions was unexpected, for, as is pointed out by Burton (17), the air insulation should change only a very small amount with temperature. However, the following considerations suggest that the difference is real.

1. Air insulations for an electrically heated boot were determined at different room temperatures. The insulation was found to be at most 10 per cent greater in the cold than in the heat. These results show that the phenomenon was not dependent on physical factors in the calorimeter nor to errors in the estimation of calorimeter temperature from measurements of room temperature.

2. The observed differences cannot be due to errors in calculation of the evaporative heat loss. Both corrections for the heat absorbed during the expansion of the water vapor, as previously described, have been calculated. The non-evaporative heat recovered has been corrected by this amount on the assumption that all of the heat absorbed by the vapor comes from the air. Both corrections lower the air insulation but do not decrease the ratio of the air insulation in the cold to that in the heat. The uncorrected ratio is 1.9. With the minimum correction it becomes 2.0 and with the maximum correction, 2.3.

3. A possible source of error is the use of average air temperature for ambient temperature instead of a suitable compromise between air and wall temperatures. Although the inner wall temperature was not measured, the thermal gradient across the walls happened to be the same under both conditions, so that the heat transfer and the thermal gradient from the outer wall to the room air must also have been identical. Analysis along these lines shows that the difference between the average air temperature in the calorimeter and the wall temperature in the two conditions could not explain the results.

4. The skin temperature measurements were subject to a known source of error produced by covering the thermocouples and thus reducing the heat loss from the covered area. This error should be greater in the heat and, therefore, the elimination of the error would increase the difference between the two conditions.

5. Since the temperature distribution on the foot varied greatly with the temperature level, the thermocouples might have been on representative areas in one condition but not in the other. For this reason the resistance thermometer previously described was used. Two new subjects spent a single night at each of the temperatures used before. The procedure was the same except for additional precautions in the measurement of air temperature. In the cold the apparent air insulation was 0.75 for one subject and 1.33 for the other. Corresponding values in the heat were 0.42 and 0.24.

Since it has not been possible to find an error in measurement or a change in the physical properties of the system which would account for the difference in the apparent air insulation between the hot and cold conditions it is suggested that the change is real and has a physiological basis.

Several explanations are possible. First, there is the familiar roughening of the skin, particularly of the exposed areas, which occurs in cold weather. This would increase the still air trapped around the skin and thus decrease the convective heat loss. The idea that such roughening is an active process occurring at temperatures below that at which 'goose flesh' becomes obvious is supported by the observations on the unusual smoothness of the skin after sectioning a cutaneous nerve (18), and after the injection of novocaine into the region of such a nerve (19).

An additional explanation is provided by the effects of curvature on heat loss. This has been considered by Van Dilla (20) with respect to the problem of clothing insulation and the treatment was extended by Burton (21) to include the air insulation around curved, insulated surfaces. Such a factor is well known to engineers. Heilman (22) gives the heat loss from bare iron pipes of different diameters, and equations relating the heat loss to the diameter of curved surfaces are given by Rice (23), who has summarized the various experimental results.

The foot and toes can be treated very roughly as a series of cylinders with the toes having approximately 15 per cent of the entire surface area. The effect of the curvature factor is such that with an equal temperature gradient from the skin to the air more heat must be lost from the toes than

from a comparable area of the rest of the foot. As has been mentioned before, the toes were the coldest part of the foot during the exposure to cold, so that little of the non-evaporative heat lost could have come from the toes. In the heat the gradient along the foot was reversed, and the toe temperature became the highest of the four measured. In this case a much greater pro-

TABLE 4. DATA FROM TABLES 1 AND 2 OF GAGGE (26), SHOWING CHANGE IN CONVECTIVE HEAT LOSS WITH CHANGING SURFACE TEMPERATURE<sup>1</sup>

CONDITION	SUBJ.	SKIN TEMP.	SKIN - AIR TEMP.	R	H	C	$\frac{C}{T_s - T_a}$
		°C.	°C.	Cal/m <sup>2</sup> /hr.			
1	I	28.9	11.8	-53	35	+18	
2	I	30.9	12.0	-18	35	-17	
3 <sup>1</sup>	I	32.3	11.2	16	34	-50	4.5
4 <sup>1</sup>	I	34.3	11.2	43	17	-60	5.4
5 <sup>1</sup>	I	34.8	10.3	86	-21	-65	6.3
6 <sup>1</sup>	I	35.3	11.1	120	-45	-75	6.8
7	I	33.5	6.1	-30	30	0	
8 <sup>1</sup>	I	34.1	6.3	5	25	-30	4.8
9 <sup>1</sup>	I	34.7	5.6	34	1	-35	6.3
10 <sup>1</sup>	I	34.4	4.8	71	-29	-42	8.8
11	I	35.3	5.8	96	-57	-39	
1	II	29.5	12.4	-57	59	-2	
2	II	30.0	11.6	-17	50	-33	
3 <sup>1</sup>	II	33.3	11.0	15	42	-57	4.8
4 <sup>1</sup>	II	34.4	11.1	49	17	-66	5.9
5 <sup>1</sup>	II	35.1	11.0	84	-6	-78	7.1
6 <sup>1</sup>	II	35.4	11.4	124	-41	-83	7.3
7	II	32.9	5.5	-27	37	-10	
8 <sup>1</sup>	II	34.4	5.9	9	29	-38	6.4
9 <sup>1</sup>	II	34.2	5.5	37	5	-42	7.6
10 <sup>1</sup>	II	34.8	5.2	72	-21	-51	9.8
11	II	35.6	6.7	98	-58	-40	

*R* represents the heat exchange by radiation. *H* is used by Gagge to describe the algebraic sum of metabolism, storage and evaporation. It has been converted from Cal/hr. to Cal/m<sup>2</sup>/hr. by the use of the surface area given for these subjects. *C*, the convective heat loss, was not given but can be obtained by the difference between *R* and *H*.

<sup>1</sup> Conditions considered by Gagge to be suitable for partitional calorimetry.

portion of the heat must have been lost from the toes. Due to this change in temperature distribution the air insulation must change in the direction which has been found.

It should be emphasized that the curvature factor does not affect the heat loss by radiation. The observed changes in air insulation are attributed to changes in the convective fraction. If this be true, such changes should

only be marked when the convective heat loss is high relative to the radiant heat loss. Insulation values have been calculated from the results of Forster *et al.* (3). For the experiments in which the hand temperature was the same as the foot temperatures in these experiments the air insulation is 1.5 Clo for the warm hand and 1.7 for the cold hand. This difference is much smaller than has been found for the foot and this may be due to the fact that the volume air flow in the hand calorimeter was only one-fifth of that used on the foot. This would limit the convective heat loss, the only fraction which could be affected by the factors which have been considered as possible causes for this change in air insulation. The convective heat loss was also very low in the experiments of Hardy and Soderstrom (24) in which the air insulation for the entire body remained constant over a wide temperature range. Hardy and DuBois (25) state that when the air movement in the calorimeter was increased that this was no longer true. However, the direction and magnitude of the changes were not given.

Some of the data of the method of partitional calorimetry indicates that the convective heat loss does not depend only on the temperature difference between skin and air and on the air movement, as is usually assumed. Gagge (26) has summarized a large number of experiments with constant air velocity in which the temperature gradient between the skin and air was maintained at either 6°C. or 11°C. while the wall temperature was varied. The data given include estimates of temperatures and amounts of heat exchange so that the convective heat loss can be calculated. Figures taken from Gagge's tables are shown in table 4. It is apparent that the convective heat loss per degree difference between skin and air is *not constant but shows* a marked trend which is correlated with the skin temperature. This is in the direction which would be expected if the factor influencing the heat loss from the foot were also important in regulating the heat loss from the entire body. If the factor responsible for these deviations is one of curvature, it might be expected that the change in air insulation of the entire body might be less than for the foot, for the data on the heat loss from pipes of different sizes show that a 50 per cent reduction in diameter is more effective in increasing the heat loss when the diameter is initially small than when it is initially large. For this reason the change in distribution of heat loss from the torso and limbs might be less effective in changing the air insulation than the change in distribution along the foot.

The curvature factor can also be used to explain the fact that in the heat the foot lost a greater amount of heat on an area basis than the entire body. While the low level of heat loss from the cold foot is that to be expected from the greater reduction of foot temperature than of general surface temperature, it is not likely that the average surface temperature of the foot was

significantly higher than the rest of the body in the heat. Since the foot has a smaller effective diameter than the entire body the increased heat loss from the foot can be assigned plausibly to the effects of curvature. However, no positive conclusions can be drawn, since the relative velocities of the air inside and outside the calorimeter were not known.

#### SUMMARY

1. The heat loss, blood flow and skin temperature of the feet were measured in two subjects living at 33°C. and at 21°C. Exposures to the two conditions lasted 2 to 7 days. Both temperatures were used in the summer and again during the winter.

2. During any one experimental period of heat the only progressive change which could be demonstrated was a gradual increase in the temperature of the toe relative to that of the rest of the foot, presumably indicating an increased blood flow in the toe. In the cold no progressive changes were found.

3. All other evidence of acclimatization appeared only as differences between the various periods of exposure to the same temperature. Exposure to cold reduced the ability of the foot to lose heat by vaporization during a subsequent period in the heat. This was associated with a decrease in the amount of heat lost by each volume of blood flowing through the foot. In some cases absence of acclimatization was associated with an increased rate of blood flow through the foot.

4. It is estimated that the foot, which has about 5 per cent of the total body area, lost 6.5 per cent of the total heat in the heat and only 3.5 per cent in the cold.

5. The heat loss per degree difference between the skin and air in the heat was about twice that in the cold. As possible explanations roughening of the skin in the cold and the effect of curvature on heat loss are suggested. Both would affect only the convective fraction of the heat loss.

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# *Pilot Metabolism and Respiratory Activity during Varied Flight Tasks<sup>1</sup>*

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METABOLISM STUDIES in aviation medicine have in the past been principally limited to observations on the effects of altitude and anoxia *per se* (1-3). The present study represents an effort to obtain information concerning fundamental physiologic responses to aircraft operation in terms of caloric output. It was undertaken in the belief that an overall evaluation of the pilot's task and his energy output might well be ascertained by the measurement of metabolic rate under a variety of flight conditions.

A Link trainer and a Piper J-3 airplane were employed and the subjects for test were intentionally selected to represent varying grades of flight experience for purposes of comparison. It was well understood that the Link trainer is quite unable to reproduce physiological responses of the same degree of intensity as those resulting from actual flight, its major drawback lying in the absence of any element of personal danger. However, it was believed that its use in studies of this nature would be justified on the basis of convenience and rigid control of all experimental conditions—desirable qualities so difficult of attainment in actual flight. The extension of the study to work with the Piper airplane served as a check upon the results obtained with the Link, as well as a source of data not hitherto available.

## METHODS

Pilot metabolism was obtained by means of mounting a standard clinical metabolism machine either on a wing of the Link trainer or within the cabin of an airplane. The arrangement of the apparatus is shown in figures 1 and 2. The machine employed was mechanically operated, thus eliminating the complications entailed by the use of an electrically-driven recorder.

All types of masks tested (oxygen mask, metabolism mask, modified gas mask) were found to leak during the flying of the various patterns desired, and a standard mouthpiece and nose-clip were finally adopted, an oxygen-

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<sup>1</sup>The experiments described were undertaken as part of a program of research performed under contract (N6ori-116) with the United States Navy, Office of Naval Research.

mask valve being inserted near the mouthpiece. This arrangement permitted the subject to shift from air to oxygen at will, and was particularly valuable when the equipment was airborne. No leakage of oxygen could be



Fig. 1. APPARATUS used to determine the metabolic rate of subjects operating a Link trainer. The machine was mounted on the right wing (not shown) and connected to the subject by tubes leading directly to the cockpit. This arrangement yielded tracings in 'flight' of equal clarity to those obtained at rest.

Fig. 2. INSTALLATION OF METABOLISM MACHINE in a Piper J-3 airplane. The pilot was afforded an unobstructed view of the instrument panel and enabled to gauge the amount of oxygen remaining in the spirometer at all times.

detected with the apparatus thus assembled, and the tracings secured were, graphically, as perfect as those obtained under normal laboratory conditions.

A total of 103 determinations was made on the 10 subjects employed in the experiment under the following conditions:

1) Standard condition. Subject abstained from food, coffee or tobacco for 12 hours. He remained seated at the controls for 15-30 minutes prior to the standard determination.

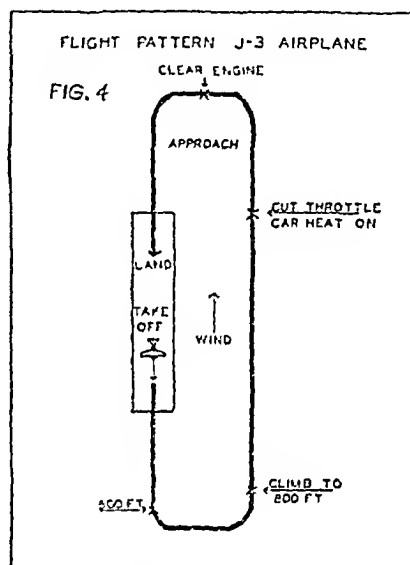
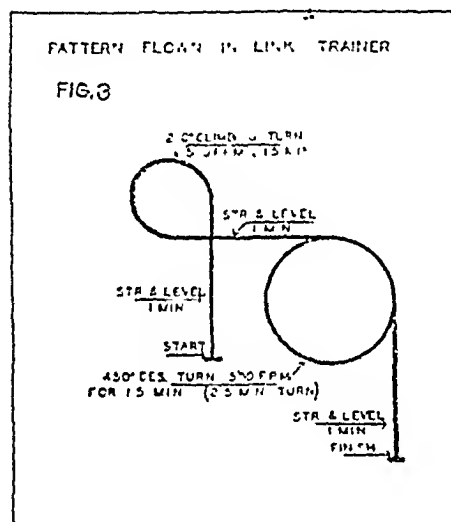


Fig. 3. PATTERN 'FLOWN' in the Link trainer. It was designed to incorporate a highly varied task requirement within a limited (7 min) time.

Fig. 4. FLIGHT PATTERN used with the J-3 airplane. It was the standard 'traffic pattern' in use at the airport where the study was conducted.

### Link trainer

2) Straight and level flight. The subject was required to hold the trainer straight and level for 8 minutes. Permissible error: 3 degrees of turn and 100 f.p.m. on vertical speed indicator.

3) Turns. Standard turns (3 degrees per second) were executed as follows:

Straight and level	1 minute
360-degree turn to the right	2 minutes
Straight and level	1 minute
360-degree turn to the left	2 minutes
Straight and level	1 minute

Permissible error: Five seconds for the 360-degree turns; 2 seconds for the straight and level flights. Vertical speed within 100 f.p.m.

4) Pattern in smooth air. The pattern shown in figure 3 was devised to contain a high degree of variation in the flight task within a short time interval. Permissible error: 3 seconds for the 270-degree turn; 6 seconds for the 450-degree turn; 200 f.p.m. in vertical speed.

5) Repetition of the pattern with the 'rough air' turned on.

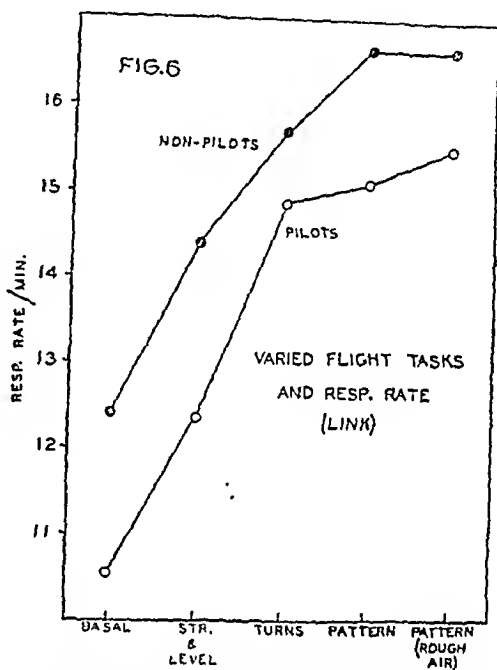
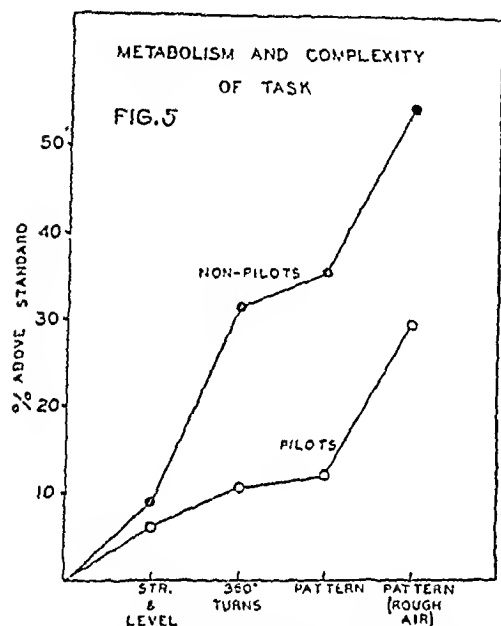


Fig. 5. EFFECTS OF INCREASING COMPLEXITY of task on the metabolic rate of pilots and non-pilots operating a Link trainer. The 'standard' rate was obtained while the subject was seated, at rest, at the controls.

Fig. 6. EFFECTS OF INCREASING COMPLEXITY of task on the respiratory rate of pilots and non-pilots operating a Link trainer.

### Airplane

6) Take-off and flying of the standard traffic pattern; approach and landing, as shown in figure 4.

7) Rectangular pattern at an altitude of 800 feet:

Straight and level.....	2 minutes
180-degree turn to the left.....	1 minute
Straight and level.....	2 minutes
180-degree turn to the left.....	1 minute

Subjects of varying flight experience were used in the experiments:

- Four veteran military aviators (av. 3,500 hrs.)
- One commercial aviator (200 hrs.)

- c) One private pilot (90 hrs.)
- d) Two student pilots (av. 40 hrs.)
- e) Two non-aviators (used in the Link trainer studies after sufficient practice enabled them to execute the patterns flown by the pilots with an equal degree of precision).

*Metabolic Responses to Link Trainer Operation.* In the work with the Link trainer, a total of 86 experiments was made, employing two veteran military aviators and two non-aviators. The results of these tests are shown in figure 5 in which the increased caloric output of the subjects is expressed in terms of percentage over the standard level. This standard metabolic rate was identical in both pairs (40 cal/sq.M/hr.). It will be noted that the metabolic rate was found to increase with complexity of task and that the magnitude of such increases was much greater in the non-pilots than in the veteran flyers. Note that the pilots, flying the pattern under these conditions (instrument), showed an increase in metabolic rate of 12 per cent compared to 37.5 per cent for the non-aviators.

When flying the pattern with 'rough air' both groups showed similar metabolic increases: 7.1 and 8.7 cal/sq.M/hr. for pilots and non-pilots respectively. Moreover, in terms of percentage, the pilots showed a figure of 11.2 percentage above their 'smooth air' rate for the same pattern against a comparable figure of 14.1 for the non-pilots. The additional work demanded of both pairs in negotiating the 'rough air' may therefore be said to be approximately the same.

It was concluded that pilot metabolism increases with increasing complexity of task, even when such tasks demand no appreciable increase in voluntary muscular exertion (example: turns as opposed to climbing turns), and that the increases in metabolic rates observed represent the increased amount of muscular tension (increased tendency to grip the controls and to tense the skeletal musculature, generally) entailed by the task at hand. The fact that the negotiation of 'rough air' (increased movement of the controls) produced similar percentage rises in both pilots and non-pilots was held to support this opinion. This increased muscular tension with consequent elevation of caloric output is measurably greater in, and characteristic of, the inexperienced (as compared to the experienced) pilot.

#### *Respiration During Link Trainer Operation*

Two hundred and seventy-four determinations of respiratory rate were made, employing two veteran pilots and two non-flyers (fig. 6). Both pilots and non-pilots exhibited an augmented respiratory rate with an increase in task complexity, although considerable individual variation was shown in this respiratory sensitivity. Thus, the respiratory rate was found to vary

during a single run as the pilot changed the attitude of the trainer from straight and level to turning flight.

The degree of respiratory sensitivity to an altered flight pattern was not, however, correlated with experience. On the average, nevertheless, shifts in respiratory rate were greater in the non-aviators. Thus, the most experienced pilot employed in the experiments (3800 hrs.; 200 hrs. Link trainer) proved to be the most sensitive to attitude changes, his respiratory rate altering abruptly from slow (av. 15/min.) to rapid (av. 18.5/min.) upon entering a turn. In this subject, return to level flight was uniformly characterized by a single, deep inspiration. These changes in the respiratory rate with the flight task were best exemplified during the flying of the patterns, as shown in figures 7 and 8. Note that in both pilots and non-pilots the respiratory rate was highest during the climbing turn, which in this case was made at an air speed very close to the stall. During the descending turn (a maneuver requiring an equal degree of precision, but with the possibility of a stall eliminated) the respiratory rate was once more elevated from that obtaining during level flight, but to a lesser degree in pilots and non-pilots as well.

It was concluded that pilot respiratory rate varies with the task performed even though such tasks may require insignificant changes in the manipulation of the controls. Since, moreover, a uniformly higher respiratory rate was found to be characteristic of climbing close to the stall, these respiratory responses to the flight task and attitude were attributed to increased 'tension' on the part of the pilot (mental concentration; gripping of the controls; generally increased muscle tension).

*Metabolism in Flight.* In these experiments the subjects were required *a*) to fly a standard traffic pattern (figure 4) and *b*) to fly a rectangular course at 800 feet altitude, the turns being standard (3 degrees per sec.) to insure uniformity of performance in so far as possible. The metabolic rates during flight were compared with the standard rate while seated in the airplane on the ground. Three pilots served as subjects (airline, commercial, student) and a total of 16 flights was made. The air was characterized as 'rough' during the tests. Careful timing of the phases of all flights was done by observers on the ground as a check on uniformity of performance and to determine the amount of time expended in ascent and descent in (*a*) above, since this was quite necessary for accurate calculations of changes in barometric pressure, and consequently in gas volume corrections.

The results of the tests in which a traffic pattern was flown are reproduced in figure 9. As in the Link trainer studies, caloric output was found to be definitely correlated with experience. The standard metabolic rate averaged

49.9 cal/sq.M/hr. in the subjects used, varying from 48.4 to 52.6. The airline, commercial and student pilots' average caloric output while flying the pattern was 81.5, 87.4 and 91.4 cal/sq.M/hr., respectively. It was concluded that this correlation in caloric output and flight experience could best be explained on a basis of muscular tension in flight. The same correlation was indicated by experiments in which a rectangular pattern was

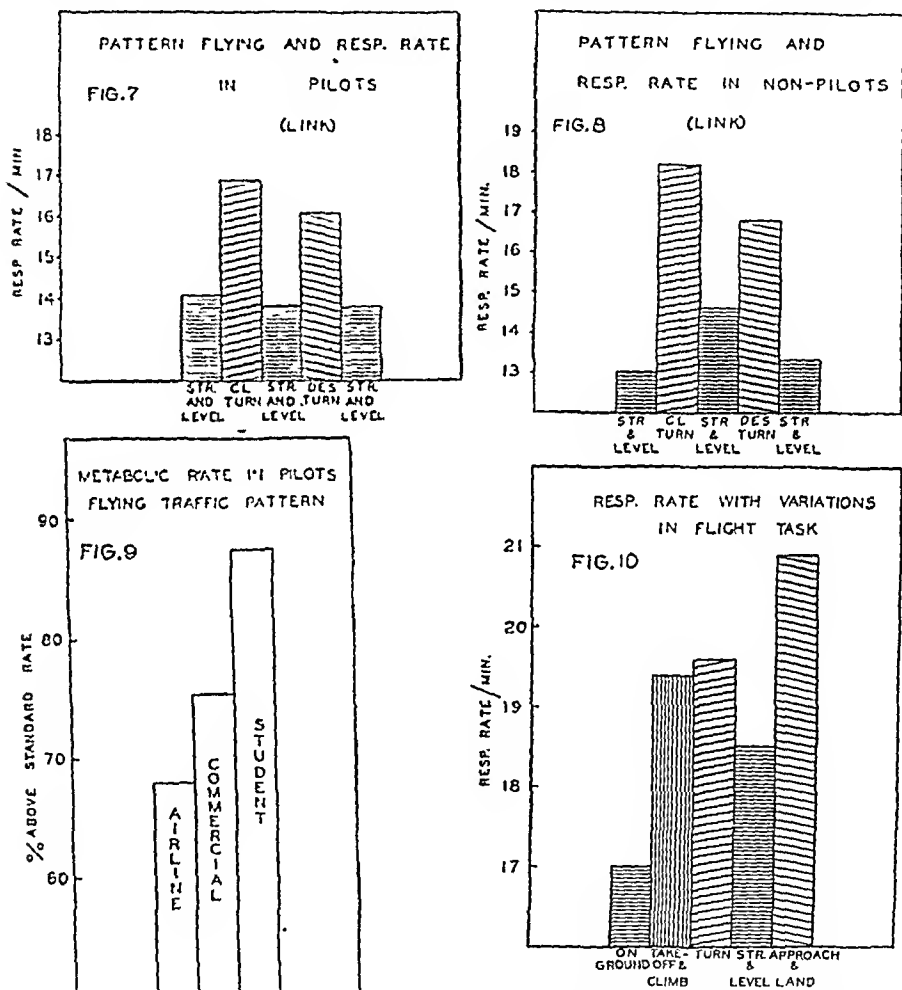


Fig. 7. EFFECTS OF PATTERN FLYING on the respiratory rate of pilots operating a Link trainer.

Fig. 8. EFFECTS OF PATTERN FLYING on the respiratory rate of non-pilots operating a Link trainer.

Fig. 9. METABOLIC RATES OF AIRLINE, commercial and student pilots flying a traffic pattern, in an airplane. The 'standard' rate was that obtained while the subject was seated, at rest, at the controls.

Fig. 10. EFFECTS OF PATTERN FLYING on the respiratory rate of airplane pilots.



flown at 800 feet. Here the caloric output of the student pilot increased by 70.2 per cent, while that of the airline pilot rose but 12.1 per cent.

*Respiratory Rate in Flight.* Changes in respiratory rate during various phases of the flight task were determined by correlating the timed tracing obtained from the metabolism machine within the airplane with time records made by observers on the ground. Figure 10 shows an average of these determinations. It was found that, as in the case of the Link trainer study, the respiratory activity of the pilots was altered by the demands of the specific flight task momentarily involved; further, that the respiratory rate was lowest on the ground before take-off and rose during take-off and the turns at the upwind limit of the pattern. During straight and level flight respiratory activity declined, but subsequently rose to its highest value during the approach and landing—a period during which demands on pilot concentration and skill are greatest.

It was concluded that respiratory activity during flight (as in Link trainer operation) varies with task complexity and is greatest during those maneuvers demanding maximum concentration, skill and judgment on the part of the pilot.

#### DISCUSSION

A review of available (unclassified) literature has failed to reveal studies comparable to the above, the majority of related observations being confined to high altitude effects (1-3) rather than applying directly to aircraft operation. Through fortuitous circumstance, a memorandum report (AAF) by Penrod (4) was obtained in which he has described a study of respiratory requirements for Link trainer flying. He found that 'rough air' increased the ventilation 'moderately'. However, in this work, pressure drop in oxygen cylinders (connected to the mask through a demand valve) was the criterion employed, and such a method cannot yield quantitative data on oxygen consumption, caloric output or the rate and depth of the respirations.

Pilot metabolism was selected for study since it constitutes a single determination, conveniently made in aircraft, which yields quantitative data on work output, oxygen requirement, muscular tension, comparative activity with varying flight tasks and the comparative difficulty of the various maneuvers executed as well as graphic records of respiratory responses to variations in task in pilots differing in experience, temperament, etc.

The Link trainer was selected as the instrument of choice (in contradistinction to the airplane) for the reason that its use permits the rigidity of control essential to obtaining valid and comparable data. Strict standards of performance may be adopted with this equipment, and all variations in indicated air speed, vertical speed, rate of turn, the time of all phases of

the 'flight', altitude, etc., may be readily observed while an accurate graphic record of each performance is secured by means of the automatic recorder or 'crab'. In an airplane in flight such strict comparisons cannot be made due to variations in the turbulence of the air and because it is impossible for the subject to duplicate exactly his successive performances. Thus, in such a simple problem as taking off and landing it is well recognized that "no two landings are alike". The best that can be done is to perform each test under as nearly identical conditions as possible with strict adherence to those procedures which are subject to control. In spite of these shortcomings of the airplane as a laboratory instrument, however, it is necessary that results obtained through other means such as the Link trainer be validated in the air, since it is the task of flying the airplane with which we are ultimately concerned, and the physiological stresses of flight can be adequately investigated only in studies involving the actual operation of aircraft.

That caloric output as well as respiratory rate and depth may be strongly influenced by psychic factors was apparent from the inception of the work. Thus, the most experienced pilot employed in the Link studies showed the most striking susceptibility to the execution of turns as evidenced by the abrupt onset of rapid and shallow respirations as the turn was entered, and one or two very deep inspirations at the conclusion of the maneuver. This respiratory pattern was invariably present. A commercial pilot expressed concern over the use of a short runway necessitated by wind conditions. Metabolic tracings secured from this man showed a notable increase in oxygen consumption and respiratory rate from the beginning of the approach to the field until ground contact was made. Again, a private pilot employed on a single occasion exhibited such an abnormally rapid respiratory rate (32/min.) when aloft that the data secured from the tests were discarded since it was considered that he could not accustom himself to the use of the metabolism machine while in flight. Experienced flight instructors expressed the opinion that this subject was one who "would not make a military aviator" due to apprehension while flying.

While the experiments described are elementary in nature and limited in number and scope, it appears quite possible that such studies may have rather far-reaching implications in such fields as pilot selection, aeroneurosis and flying fatigue. At present, adaptability to the task of flying as well as the degree of tension under which the pilot may labor are estimated by clinical examination, aptitude tests and other means of a subjective nature. If it should be found that quantitative measurements of caloric output are, indeed, reliable criteria for gauging the stresses and strains of flight, further experiments of this nature should prove well worth while.

## SUMMARY

1. Pilot metabolism was found to increase with increasing complexity of flight task, and such increases were measurably greater in the inexperienced as compared with the experienced pilot.

2. The respiratory rate of pilots was found to vary with the task performed. These variations were in the same direction in inexperienced and experienced subjects.

3. The observed increases in metabolism and respiratory rate were not invariably correlated with the amount of muscular activity essential to the execution of the maneuvers executed, and were attributed to generalized increases in skeletal muscle tension.

4. The phenomena summarized above were observed both in Link trainer operation and in flying an airplane.

5. The implications of these observations in aviation medicine, generally, are discussed.

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# Arterial Blood Gases during Pressure Breathing at Simulated High Altitudes<sup>1</sup>

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RECENT ADVANCES in aircraft design have made possible attainment of altitudes in which man is unable to live, even while breathing pure oxygen. This difficulty has been overcome by the development of pressurized cabins and, to some extent, by the use of pressure-breathing equipment. The latter effectively increases alveolar oxygen tension; however, there has been some uncertainty as to whether, in the presence of the unusually high intrapulmonary pressure increment, the expected increase of arterial oxygen saturation actually occurs. Likewise, there is uncertainty as to whether carbon dioxide exchange and acid-base equilibrium remain within normal or reasonable limits. To test these points we have studied the oxygen saturation, carbon dioxide content and pH of the arterial blood of young men during pressure breathing at rest, at simulated high altitudes in a low-pressure chamber.

Two types of pressure-breathing equipment were used. With either system, pulmonary pressure was positive during both the inspiratory and the expiratory phases of respiration.

A. *Positive Pressure Breathing with Counterpressure.* Counterpressure is provided by means of a jacket-like rubber bag which encircles the entire trunk of the subject. A flight jacket attached to, and worn over, the bag serves to give rigidity to its outer wall. Oxygen is supplied on the closed-circuit principle, first to the bag at the desired pressure, and thence to the subject through a suitable mask. During inspiration the volume of the bag decreases, allowing for chest expansion; during expiration the air from the lungs passes through carbon dioxide absorbent and back into the bag, increasing the volume of the latter. Because of these compensating effects, the positive pressure during both inspiration and expiration varies relatively very little, and pressures as great as 30 mm. of mercury may be tolerated with little fatigue. See diagram in figure 1.

B. *Positive Pressure Breathing Without Counterpressure.* Oxygen is supplied directly to the mask through a 'pressure demand' regulator, by means of which the pressure of

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<sup>1</sup> The work described in this paper was done at Mayo Aero Medical Unit under the direction of Dr. W. M. Boothby, under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Mayo Clinic, and also a contract between the Air Materiel Command, Wright Field, Dayton, Ohio, and the Mayo Clinic, Rochester, Minnesota. The experiments were completed in the spring of 1943.

<sup>2</sup> On assignment in the Division of Aviation Medicine, Mayo Foundation, from the Army of the United States.

inhaled gas may be adjusted manually to any value between 0 and 27 mm. of mercury. Expiratory pressure is maintained at a value just slightly greater than inspiratory pressure by means of a compensated valve in the mask. The variation of positive pressure between inspiration and expiration may be somewhat greater than in the preceding method, and the actual values will be dependent on the flow characteristics of the demand and expiratory valves used in any particular experiment.

#### PROCEDURE AND RESULTS

The subjects employed were healthy men, aged 18 to 32 years. Each subject was thoroughly trained in the use of the breathing equipment and the details of procedure by means of practice 'flights' in the low-pressure chamber. The sequence of events during an experimental flight was as follows: The breathing equipment was fitted and tested for leaks, the subject assumed the recumbent position, and the earpiece of a Millikan oximeter (Coleman model 17, no. 4769) was attached to his ear. The oximeter was adjusted<sup>3</sup> to indicate 100 per cent oxygen saturation while the subject breathed oxygen at 2 mm. positive pressure for 15 to 20 minutes before ascent in order to obtain partial denitrogenation. 'Ascent' was then made at the rate of 2,000 to 4,000 feet per minute to a pressure equivalent to an altitude of 40,000 feet, while the subject continued to breathe oxygen at 2 mm. positive pressure. At this altitude breathing and chamber pressures<sup>4</sup> were readjusted to the particular values to be studied. After one to 24 minutes under these conditions a 15 cc. sample of arterial blood was collected by puncture of the femoral artery at a previously anesthetized site about 1 cm. distal to Boupart's ligament. At the same time the oximeter reading of percentage saturation was taken. The blood sample was drawn into a syringe containing a disklike glass bead for mixing, 1 to 2 mgm. of heparin (110 units per milligram) as anticoagulant and oil just sufficient to fill all air spaces. Immediately after its collection the sample was sealed in the syringe, mixed, placed in ice water and brought to ground pressure in the chamber air lock.

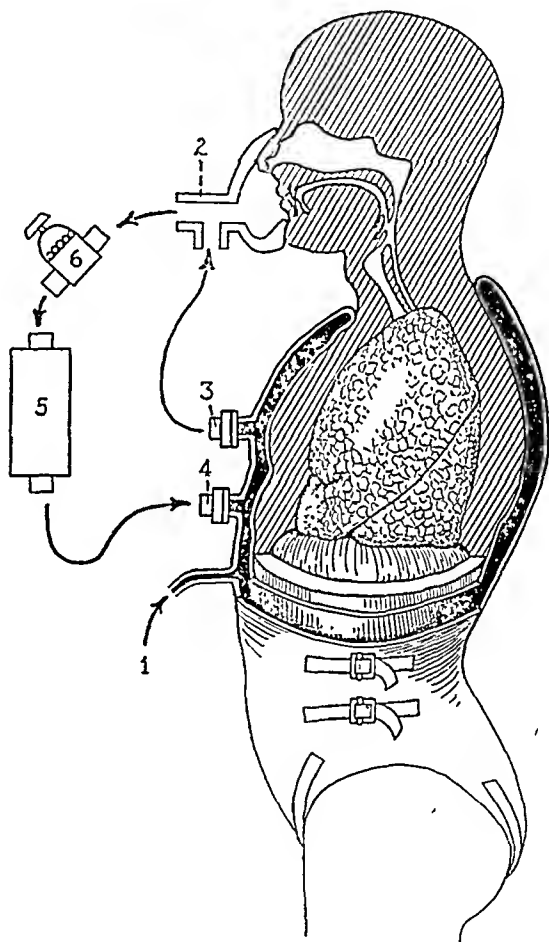
Determinations of pH were made at 38°C. by means of the capillary glass electrode described by Dill, Daly and Forbes in conjunction with a Coleman pH meter, model 4, reading to 0.1 millivolt. The glass electrode was calibrated with the phosphate buffers of Hastings and Sendroy before and after each determination of pH. Blood gases were determined by the manometric methods of Van Slyke and Neill, corrections for physically dissolved oxygen being estimated from the data of Sendroy, Dillon and Van Slyke. The blood samples were kept at 0°C. until they could be analyzed. Determinations of pH were completed usually within 10 to 15 minutes, at

<sup>3</sup> Errors in oximeter readings due to static electricity were avoided as far as possible by provision of adequate moisture within and without the low-pressure chamber.

<sup>4</sup> Chamber pressures were measured by means of a mercury barometer which had been calibrated by the Bureau of Standards.

most 30 minutes after arterial puncture. Determinations of oxygen and carbon dioxide were completed within an hour or two, at most four hours. Carbon dioxide tension was calculated by application of the Henderson-Hasselbach equation to values for plasma carbon dioxide content, which, in turn, were derived from those of whole blood by means of the line chart of Van Slyke and Sendroy. Oxygen tension was estimated by reference to

Fig. 1. DIAGRAMMATIC SKETCH SHOWING PRESSURE-BREATHING VEST (COUNTER-PRESSURE) SYSTEM. Oxygen enters the jacket from a constant pressure demand or constant flow regulator (1). The mask (2) is connected to the pneumatic jacket by two pieces of corrugated tubing with an inspiratory (3) and an expiratory (4) valve at the connections to the jacket and with a container (5) for sodium hydroxide (Shell Natron) on the expiratory tube. On inspiration oxygen passes from the jacket through the inspiratory tube to the mask (2) and into the lungs. Gas from the lungs is exhaled through the expiratory tube to the Shell Natron container (5) and then back into the pressure jacket through the expiratory valve (4). The total pressure in the system is regulated by a spring-loaded relief valve (6) to maintain any desired pressure in the system from 0 to 30 mm. of mercury. An even pressure is maintained throughout the system because gas entering the lungs comes from the jacket and goes into it again with exhalation.



oxygen dissociation curves for human blood based on data of Dill (12). Errors in determination of percentage oxygen saturation of blood, recently pointed out by Roughton and his associates, will appear as relatively small errors in oxygen tension, since the oxygen saturation of most of the samples was less than 85 per cent.

The data obtained from analysis of 20 blood samples taken during experiments with counterpressure, and of 13 samples taken during experiments without counterpressure, are shown in parts A and B, respectively,

of table 1. The data are arranged roughly, first in the order of increasing altitude, second in the order of increasing pulmonary pressure at each altitude and third in the order of increasing time spent under each combination of these variables. Blood samples collected during a given experimental 'flight' are designated by the same experiment number.

*Oxygen Saturation.* At 46,000 feet, the breathing of oxygen at ambient pressure only, that is, at zero positive pressure, leads to markedly deficient oxygenation. Blood samples 2, 3 and 4, taken under these conditions, revealed saturations of 71.9, 58.4 and 71.4 per cent, mean 67.2. With 15 mm. positive pressure at this altitude, oxygenation is considerably improved: in nine samples from four subjects in experiments with counterpressure, percentage saturation ranged from 68.9 to 87.4, mean 77.0; and in 12 samples from eight subjects in experiments without counterpressure, saturation ranged from 69.1 to 85.0, mean 78.2 per cent. Five of the blood samples were taken after the subjects had breathed against 15 mm. pressure for 15 to 24 minutes. Breathing against pressures greater than 15 mm. was not attempted without counterpressure, but several blood samples were obtained during breathing at higher pressures with counterpressure. Of these, four samples from three subjects breathing at positive pressures of 29 to 34 mm. at 46,000 feet showed a very satisfactory degree of oxygenation, 88.0 to 95.6 per cent. At 50,000 feet three samples from one subject breathing at 33 and 32 mm. pressure were found to be 75.9 to 77.0 per cent oxygenated. In 27 (82 per cent) of the 33 measurements oximeter values agreed with corresponding gasometric values for oxygen saturation to within  $\pm 6$  per cent saturation. The remaining six oximeter measurements were unaccountably much too high, ranging from 7 to 20 per cent saturation higher than gasometric values.

*Carbon Dioxide and pH.* In 21 samples obtained at 46,000 feet and 15 mm. positive pressure the mean carbon dioxide content was 46.1 volumes per 100 cc. of plasma, range 42.9 to 49.7; mean pH was 7.45, range 7.40 to 7.52. These values are, in the case of carbon dioxide, somewhat lower, and in the case of pH definitely higher, than was observed by Gibbs and his associates in the arterial blood of 50 normal young men at rest at sea level. These investigators found the mean carbon dioxide content to be 48.2 volumes per cent, range 44.6 to 50.4, and the mean pH to be 7.424, range 7.374 to 7.449. At higher breathing pressures, ranging from 29 to 34 mm., the few analyses obtained at 46,000 and 50,000 feet indicate that shifts of carbon dioxide content and pH tend to be somewhat greater than those observed when the breathing pressure was 15 mm.

*Partial Pressures of Oxygen and Carbon Dioxide.* On the assumption that the calculated values for the arterial tensions of these gases also represent alveolar tensions, their sum has been combined with the alveolar water

vapor tension, .47 mm., for comparison with total oxygen pressure, that is, with the sum of barometric pressure plus breathing pressure, to which the sum of the alveolar pressures must necessarily be equal. These summations, which will be found in the last two columns of table 1, show very good agreement in most instances, indicating that the assumption of near equality of arterial and alveolar partial pressures is probably justified for the conditions of pressure breathing employed. (Recent data indicate that this assumption, which has long been accepted for carbon dioxide and for oxygen at low pressures, is now to be considered valid for oxygen even at sea level.) It appears that the various readjustments imposed by increased pulmonary pressure are not such as to disturb these relationships seriously.

#### COMMENT

The foregoing data suggesting probable equality of arterial and alveolar oxygen tensions during pressure breathing are derived indirectly from observations on arterial oxygen saturation and imply, in turn, that the altitude tolerance gain, so far as arterial oxygen is concerned, is that to be expected from the increased pressure of oxygen supplied. Unpublished observations on pressure breathing made in other laboratories are in agreement that, on the average, this relationship holds. Comparison of the present data with those of Dill and Hall, which refer to respiration at ambient pressures at high altitude, leads to a similar conclusion. These investigators observed that the breathing of oxygen at 43,200 feet, barometric pressure 121 mm. of mercury, resulted in arterial saturation of 77 per cent. In our experiments a similar average saturation, 77.7 per cent, was observed in the 21 tests conducted at 46,000 feet (barometric pressure 106 mm. of mercury), with 15 mm. of mercury positive breathing pressure, where total oxygen pressure was also 121 mm. of mercury, that is, 106 plus 15. Thus the degree of oxygenation to be expected at a given oxygen pressure was substantially realized under the conditions of pressure breathing employed. Comparisons of this sort are valid only if the carbon dioxide pressures in the experiments compared are closely the same. This was not the case in some of the experiments at the higher breathing pressures, for example, in four experiments at 46,000 feet (106 mm.) and 29 to 34 mm. positive pressure. Taking 32 mm. as the average intrapulmonary pressure, total oxygen supply pressure in these experiments was 138 mm., which corresponds, in the data of Dill and Hall, to an altitude of 40,400 feet and oxygen saturation of about 87 per cent. The mean of the observed saturations was, however, 93.3 per cent, a value noted by Dill and Hall for pure oxygen at about 37,000 feet. This degree of oxygenation indicated an apparent altitude gain of 9,000 feet as compared with a gain of 5,600 feet predicted from total oxygen pressures. The failure of the prediction to agree in this instance is obviously due to the



TABLE 1. GASEOUS CONSTITUENTS OF ARTERIAL BLOOD AT EXTREMELY HIGH SIMULATED ALTITUDES<sup>1</sup>

TABLES.

EX- PERI- MENT	SUBJECT	ALTI- TUDE	POSITIVE PRESSURE BREATHE	TIME UNDER EXPERI- MENTAL CONDI- TION BEFORE PUNC- TURE	pH	CO <sub>2</sub> CON- TENT	O <sub>2</sub> CAPAC- ITY	O <sub>2</sub> CON- TENT	O <sub>2</sub> SATU- RATION		CALC. TENSIONS			BARO- METRIC PRES- SURE + POSITIVE PRES- SURE
									Gasometric	Oximeter	pO <sub>2</sub>	pCO <sub>2</sub>	pO <sub>2</sub> + pCO <sub>2</sub> + pH <sub>2</sub> O	
		thou- sands of ft.	mm. Hg	min.		volume percent			%	%	mm. Hg			
A. With counterpressure														
1	CBT	41	15	9.6	7.41	46.7	19.9	17.9	90.0	97	62	38	147	149
2	CBT	46	0	1.1	7.48	42.1	20.6	14.8	71.9	76	35	30	112	106
3	WLB	46	0	1.8	7.46	48.2	21.4	12.5	58.4	60	28	36	111	106
4	CBT	46	0	2.2	7.46	42.3	20.6	14.7	71.4	76	35	32	114	106
9	RE	46	15	1.1	7.46	48.4	19.2	14.2	74.0	89	38	36	121	121
9	RE	46	15	2.2	7.42	48.7	19.3	13.3	68.9	89	36	39	122	121
2	CBT	46	15	1.7	7.46	43.1	20.5	17.9	87.4	89	53	32	132	121
6	RE	46	15	2.8	7.44	47.6	19.3	14.8	76.7	89	41	37	125	121
4	CBT	46	15	3.3	7.47	44.2	20.4	16.8	82.4	84	45	32	124	121
8	HH	46	15	3.6	7.47	43.9	19.7	15.4	78.2	79	41	32	120	121
5	HH	46	15	6.3	7.44	44.6	20.9	16.1	77.0	83	41	35	123	121
7	WLB	46	15	7.1	7.49	48.1	20.3	14.9	73.4	74	36	34	117	121
8	HH	46	15	21.1	7.44	46.1	20.2	15.2	75.3	74	39	36	122	121
9	RE	46	29	0.5	7.45	47.1	19.2	16.9	88.0	98	54	35	136	135
2	CBT	46	31	1.0	7.49	40.4	20.5	19.4	94.6	98	69	28	144	137
7	WLB	46	32	1.9	7.49	43.6	20.6	19.7	95.6	93	76	30	153	138
4	CBT	46	34	4.0	7.52	38.9	20.3	19.3	95.1	95	70	25	142	140
10	CBT	50	33	5.2	7.46	44.5	20.6	15.8	76.7	77	40	33	120	121
10	CBT	50	32	10.5	7.46	42.9	20.5	15.8	77.0	76	40	32	119	119
10	CBT	50	32	15.3	7.46	42.7	20.7	15.7	75.9	77	39	32	118	119
B. Without counterpressure														
1	MH	44	13	4.4	7.49	44.5	21.0	18.6	88.5	91	53	31	131	128
2	CBT	46	15	0.3	7.52	43.7	19.6	16.4	83.7	85	44	29	120	121
5	DD	46	15	2.5	7.43	49.7	18.7	14.3	76.5	78	41	39	127	121
3	DB	46	15	2.8	7.48	47.3	18.8	15.0	79.7	78	42	33	122	121
4	SCA	46	15	3.0	7.44	42.9	19.0	15.4	81.0	79	45	33	125	121
6	JM	46	15	3.0	7.46	46.0	20.6	16.5	80.0	83	43	34	124	121
7	HH	46	15	3.6	7.44	45.1	19.4	14.7	75.8	78	40	35	122	121
8	RE	46	15	3.7	7.43	46.5	17.8	13.4	75.2	77	40	36	123	121
1	MH	46	15	7.8	7.51	44.9	20.7	17.6	85.0	86	46	30	123	121
2	CBT	46	15	15.0	7.46	45.0	19.5	14.9	76.4	81	40	31	118	121
5	DD	46	15	19.0	7.40	49.2	19.1	13.2	69.1	73	36	41	124	121
6	JM	46	15	22.0	7.44	45.0	20.6	17.0	82.5	77	46	35	128	121
8	RE	46	15	23.6	7.44	46.8	17.3	12.7	73.4	78	38	35	120	121

<sup>1</sup> Subjects at rest, breathing pure oxygen against positive pressure.

fact that a considerably greater reduction of alveolar carbon dioxide tension developed in these experiments than in the majority of those at 15 mm. positive pressure.

The various factors that may cause reduced alveolar carbon dioxide tension in pressure breathing are not clearly understood. Anoxia, which leads to hyperventilation and hence to more or less reduced alveolar carbon dioxide tension and elevated blood pH, was not present in the four experiments at an average of 32 mm. pressure just mentioned; yet the reductions in  $p\text{CO}_2$  and increases in pH were as large as in any of the experiments in which anoxia was present. Hyperventilation, in the ordinary meaning of the term, may not have been the only important factor in these experiments. Recent observations by Bateman in this laboratory on pressure breathing in room air at ground level, in which again anoxia could not be a factor, likewise have demonstrated that transient decreases in alveolar carbon dioxide tension occur in some subjects. Comparison of the effect with that from ordinary hyperventilation indicates that it does not represent exclusively an overventilation acapnia. Whatever the mechanism may be, it appears, in the present series of observations, that the reduction of alveolar carbon dioxide pressures and increases in pH have not been excessive. In some subjects, such as C. B. T., the changes develop more consistently than in others. Usually the shifts are most marked at the beginning of pressure breathing; subsequently, more or less effective compensation develops, so that carbon dioxide tension and pH do not alter to dangerous levels.

The degree of arterial oxygen saturation attained by breathing oxygen at 15 mm. pressure at 46,000 feet obviously is insufficient to maintain normal physiologic efficiency. However, practical experience as well as tests of psychomotor performance indicate that limited physical and mental activity can be accomplished by many individuals during pressure breathing at altitudes which otherwise could not be tolerated. Tolerance to these high altitudes is frequently determined by other factors than oxygen supply or mental efficiency, such as susceptibility to the 'bends' or the 'chokes.' Adequate selection and training of subjects is therefore essential. We have not observed significant differences in oxygenation when the subjects were breathing with or without counterpressure. However, when the counterpressure jacket is used, respiration is much less fatiguing and higher intrapulmonary pressures may be used.

#### SUMMARY

The oxygen saturation, carbon dioxide content and pH of arterial blood have been measured in young male subjects exposed to pressures equivalent to altitudes of 41,000 to 50,000 feet while they were breathing oxygen at increased intrapulmonary pressures ranging from 0 to 34 mm. of mercury.

No differences were observed between data collected with and without counterpressure; however, the use of a counterpressure jacket rendered breathing less fatiguing, especially at the higher intrapulmonary pressures.

The data suggest that arterial oxygen and carbon dioxide partial pressures attain equality with their alveolar partial pressures, respectively, just as they do during normal respiration at high altitudes. Reduction of alveolar carbon dioxide and shift of pH toward the alkaline side occurred in some of the subjects. These changes, which were usually more conspicuous at the beginning of pressure breathing than later, were minimal at 15 mm., somewhat greater at pressures of 30 mm. or more. Hyperventilation, in the usual meaning of the term, is probably not the exclusive cause.

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# *Reflex Sweating and the Inhibition of Sweating by Prolonged Arterial Occlusion<sup>1,2</sup>*

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**A**LTHOUGH REFLEX SWEATING responses have long been recognized, the precise nature of such responses is far from clear. Generalized body sweating may be induced by exposure of the body to environmental temperatures sufficiently high to raise the temperature of circulating blood. Autonomic centers in the brain stem, or centers in the spinal cord, are known to bring about profuse sweating when perfused with blood at high temperatures (1). We have observed that reflex sweating may also be induced by exposure of a very limited area of skin to radiant heat, and it appeared doubtful that increases in blood temperature could be responsible.

Employing a technique previously described for studying quantitative changes in the number of functional sweat glands (2, 3) this problem and the relationships of sweating and blood supply have been studied.

Measurements of sweat gland activity during normal sweating responses to high environmental temperatures show that alternating periods of high and low sweating activity occur similarly on both arms. Although such spontaneous peaks of sweating occur approximately simultaneously when measured on similar areas of both arms, they do not always occur exactly so and not always in the same intensity. These findings confirm the existence of bilateral control of normal sweating responses to high temperatures.

As radiant heat is applied to a relatively large area of one arm (10 to 20 sq. cm.) sweating first appears in the locally heated area of highest temperature. Sweating may then spread to neighboring areas of the same arm and if heat is sufficiently extreme and applied to a large area, sweating appears on the opposite arm (2, 3).

The question then arises, under what circumstances does sweating appear on areas adjacent to the heated area and on the opposite arm, and is

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there any segmental relationship to reflexly induced sweating on opposite sides of the body?

#### PROCEDURES AND RESULTS

In checking the distribution of reflex sweating when radiant heat was applied to one arm only, long strips of paper were simultaneously applied around the complete circumference of the 'reflex' arm at the wrist and upper arm. Since segmental distribution of spinal nerves to the skin of the arm involves relatively long and narrow areas extending longitudinally down the arm, a paper strip wrapped around the circumference of the arm covers several segmentally innervated dermatomes. Such dermatomes in the circumference of the upper arm derive innervation from spinal nerves  $C_5$ ,  $C_6$  and  $T_2$ , while those in the wrist are innervated by  $C_6$ ,  $C_7$  and  $C_8$ . Heat was applied to the ventral surface of the wrist of the opposite arm. Peaks of sweating were reached simultaneously on all surfaces of the circumference of both the wrist and upper arm on the reflex side and the subject often volunteered that he "felt sweating all over his body". There were consistently fewer glands participating in the peaks of sweating activity on the upper arm when compared with the wrist surfaces, and in some experiments there were times when a few glands were active on the wrist but none at all on the upper arm. There is evidence that sweating is less readily elicited on the upper arm when compared with more distal areas of the arm and hand. Sweating disappeared entirely from the upper arm and decreased markedly on the wrist of the 'reflex' arm immediately after removal of the heat stimulus from the opposite arm. Although the number of actively secreting glands steadily declined, sweating usually persisted in the heated area for a few moments after the heat was turned off.

Although all surfaces of the 'reflex' arm may participate in sweating responses to heat applied to the opposite arm, sweating is usually not as profuse on the 'reflex' side. That is, the output per gland is less and, provided the heat stimulus is not severely painful, the number of active glands is less on the 'reflex' side. It is true, however, that nearly the maximal number of glands for a given area may be activated by painful and psychic stimulation as well as by excessive heat over a large area of the body. It is suggested by Kuntz (1) that generalized sweating due to local heating is probably due to changes in blood temperature. In order to determine whether sweating responses such as those described above are actually of nervous origin or due to heating effects at the sweat centers and gland cells themselves, an arm cuff was placed around the upper arm on the 'reflex' side. This cuff was then rapidly inflated to levels above systolic pressure and radiant heat applied locally to the opposite arm. Profuse sweating in both the locally heated area and on the 'reflex' (occluded) arm occurred with the application of heat.

The necessity of heating effects at gland cells themselves was thereby ruled out.

The possibility of temperature increases at sweat centers in the brain and spinal cord remained. A cuff was therefore rapidly inflated to levels above systolic pressure around the upper arm on the heated side. Blood

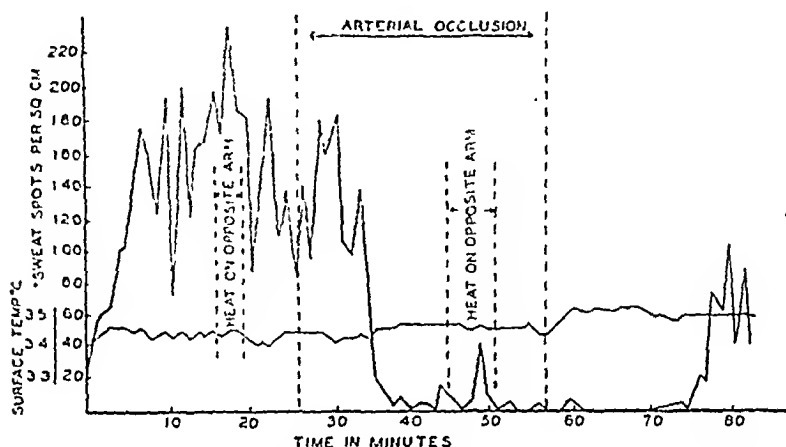


Fig. 1. SWEATING AND SKIN TEMPERATURE RESPONSES to prolonged arterial occlusion. Room temperature  $31\text{--}32^{\circ}\text{C}$ . during summer months.

could thus neither enter nor leave the area warmed by radiant heat, and again sweating was widely distributed over both the locally heated area and over the opposite ('reflex') arm. With the cuff still inflated, the heat was turned off and sweating on the 'reflex' arm immediately decreased or stopped. Sweating on the heated (occluded) arm persisted longer than in the normal, non-occluded arm presumably because accumulated heat set up local sweating responses. That reflex sweating may be induced, therefore, by stimulation of peripheral receptors without participation of temperature increases at the sweat centers in the central nervous system via the circulation of 'warmed blood' is thus conclusively demonstrated.

*Influence of Arterial Occlusion.* Sweating has been reported in the amputated human limb following electrical stimulation of the nerves (4). That sweating may occur in the absence of circulation is thus established, but sufficient information on the duration of such responses and the results of arterial occlusion in a normally sweating extremity is lacking.

Figure 1 illustrates the sweating responses during prolonged arterial occlusion. The environmental temperature was relatively high ( $31^{\circ}$  to  $32^{\circ}\text{C}$ .) and sweating was profuse throughout the control period, although a still greater number of sweat glands were reflexly stimulated into activity by application of radiant heat to the opposite arm. In order to prevent

venous congestion, arterial occlusion was accomplished by rapid inflation of an arm cuff around the upper arm from a pressure reservoir. Sweating patterns remained essentially unchanged for 6 to 7 minutes after which the number of functional glands progressively declined to very low levels. It is apparent however that cyclic phases persist even though the total number of active glands is considerably decreased. After 10 minutes of depressed sweating on the occluded arm radiant heat was applied to the opposite arm

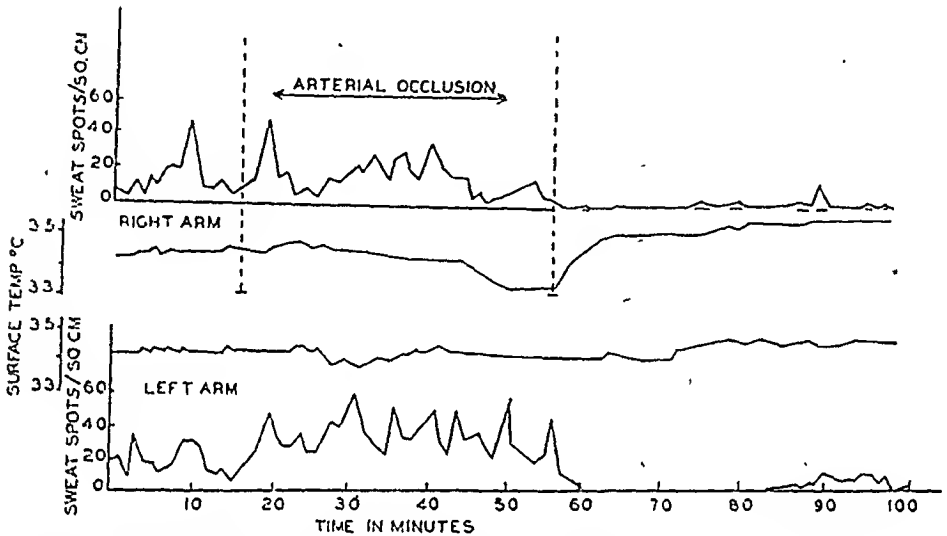


Fig. 2. SIMULTANEOUS SWEATING AND SKIN TEMPERATURE RESPONSES on right and left arms with unilateral arterial occlusion. Room temperature 26 to 27°C. during winter months.

in the same manner as in the control period. A low peak of sweating on the occluded arm represents a reflex sweating response of considerably lower order than that occurring during the control. The fact that relatively few glands responded to the same stimulus which had previously induced a profuse response indicates an alteration in irritability of the sweating mechanism. That the depressed irritability was confined to the ischemic area was indicated by a profuse, generalized sweating response on other body surfaces during the application of heat. It is true, however, that in some experiments peaks of sweating as high as those observed in the normal were obtained by application of heat directly to an area in which sweating was reduced during prolonged arterial occlusion. In such experiments however, the stimulus was applied to the ischemic area directly and was therefore considerably stronger than that occasioned by reflex stimulation. The possibility of responses of the sweat glands to the direct stimulating action of heat cannot be eliminated in these experiments.

During the later stages of the occlusion, all sensation and motor control in the ischemic arm was depressed. In testing sensation and movement, the subject was not aware the arm was stimulated unless he visually observed

application of the stimulus. The arm was intensely cyanotic but due to the high environmental temperature and absence of sweating was not cold.

After sweating had again decreased following reflex stimulation, the arm cuff was deflated. The arm immediately became intensely hyperemic and

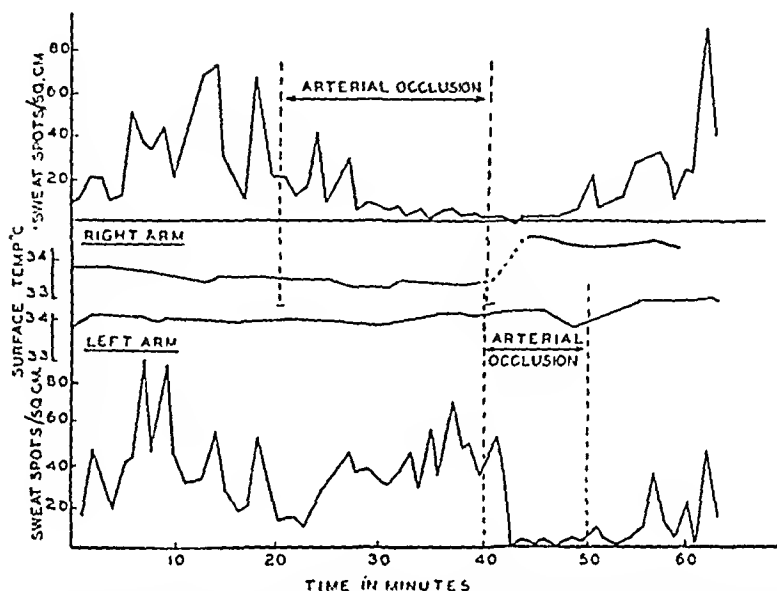


Fig. 3. SWEATING AND SKIN TEMPERATURE on right and left arms during unilateral occlusion with occlusion of 'control' arm 15 seconds before release of cuff from 'experimental' arm. Room temperature 29-30°C. during winter months with stimulation of sweating by radiant heat applied to both shoulders throughout experiment.

the skin temperature rose sharply, but sweating remained at low levels (zero for 9 minutes) for 17 minutes before cyclic responses were spontaneously reestablished.

Such experiments establish the fact that sweating does not immediately stop following arterial occlusion. Cyclic sweating continues but with decreasing numbers of glands until very low levels are attained. Even at this point many sweat glands retain secretory ability as attested by the peaks of sweating which may be attained through direct or reflex stimulation.

#### DISCUSSION

Simultaneous observations of sweat gland activity on the normal, non-occluded arm demonstrate that cyclic sweating continues at normal or slightly elevated levels throughout the period of occlusion. In other words, the central sweating mechanism continues to discharge impulses in a cyclic fashion suggesting that the site of depression is distal to the arm cuff.

The fact that the sweat glands could respond to strong reflex or to direct heat stimulation would suggest the site of depression was not primarily in



the sweat glands themselves. It would seem possible that deprivation of oxygen is the factor responsible for depressed activity and that the nerve endings (and possibly the axons) are the site of depression. Such theoretical reasoning receives support from the recent work of Wright (5) who found that excised, anoxic mammalian nerve fibers show 90 to 100 per cent reduction of action potential within 20 minutes. Wright also showed that no change occurs in action potential or polarization in mammalian nerves (cat and rabbit) for 3 to 10 minutes following exposure to an atmosphere of nitrogen. Following this period, a simultaneous depolarization and reduction in action potential proceeds rapidly for 10 to 20 minutes. It is striking that a very similar time course in depression of sweating follows deprivation of blood supply to the intact sweating mechanism. It is of historical interest that Kendall and Luchsinger (4) observed that sweating could be elicited on the dog's and cat's paws 'for the first quarter-hour' after amputation.

The prolonged depression of sweating following return of blood to the arm upon release of the occlusion pressure was somewhat surprising and suggested that factors other than, or in addition to, anoxia may be operating in preventing sweat gland activity. Figure 2 illustrates the fact that although sweating is depressed in the occluded arm, it continues at relatively normal or somewhat elevated levels on the non-occluded arm until circulation in the occluded arm is restored. Synchronous cyclic sweating was evident on both arms until late in the occlusion period when sweating in the ischemic area was definitely depressed. At this time two voluntary, deep breaths induced a comparatively high peak on the normal side with only a delayed, low peak on the occluded side. Although absolute zero levels were not observed in sweating in the ischemic arm, gradual depression was apparent during the latter part of the experiment.

When circulation was restored the skin of the ischemic arm became intensely hyperemic and warm and a severe sensation of intense pressure developed. No such obvious changes were noticeable on the normal, control arm, but attention is particularly directed to sweating responses. Immediately following deflation of the arm cuff, sweating stopped on both arms and remained depressed for 30 minutes in spite of the fact that skin temperatures continued elevated on the experimental arm and normal on the control arm. At the end of this period, voluntary deep breathing induced low-grade sweating responses in the two arms.

Such experiments suggest the possibility that during prolonged occlusion some substance may be released by ischemic tissues which depresses sweating. When this substance is released into the general circulation, sweating in other areas of the body is depressed. It remains to be determined whether such a hypothetical substance is active centrally or directly on the peripheral sweating mechanism.

Accordingly, experiments were carried out in which an arm cuff was inflated around the upper arm on the control side 15 to 30 seconds before the occlusion on the experimental arm was released. Figure 3 illustrates such a procedure. Depression of sweating during arterial occlusion is evident on the occluded arm while sweating continues prominently on the control arm. The inhibition of sweating on the control side following release of the cuff from opposite arm, in spite of the fact that circulation was arrested, indicates that the site of depression is central to the arm cuff.

Thus following a purely local inhibitory effect with little or no generalized depressant influence during the occlusion of one arm, generalized inhibition occurs upon release of some humoral agent into the systemic circulation. The inhibitory influence may be peripheral (directly upon the post ganglionic endings and the sweat glands themselves), but that this is not necessarily true is demonstrated by experiments such as those illustrated in figure 3. This leaves the possible locus of inhibition in the CNS or at the synapsis in autonomic ganglia.

#### SUMMARY

Local application of radiant heat to a restricted region of one arm induces reflex sweating responses on all surfaces on the opposite arm as well as on the heated arm. Such responses are not necessarily dependent upon heating effects in the central nervous system or the sweat glands themselves as indicated by persistence of reflex sweating in spite of occlusion of the blood flow from the heated arm.

During arterial occlusion, sweating may continue relatively unchanged for the first 5 to 15 minutes. Following this period there is a progressive decline in the number of functional sweat glands although cyclic phases of sweating continue until low levels of sweating are attained. Simultaneous observations on the opposite, 'control' arm during the period of occlusion show normal cyclic sweating, usually at a somewhat elevated level. Immediately upon release of the occlusion, the ischemic arm becomes hyperemic and warm, with no noticeable change in temperature on the control arm, but sweating on both arms is markedly inhibited. Such inhibition occurs on the 'control' arm even though the circulation is clamped off immediately prior to the release of the occlusion. An unknown humoral agent produced by ischemic tissues and acting centrally to depress sweating therefore is indicated.

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# *Tropical Fatigue and Warfare*

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**H**ISTORY ABOUNDS in examples of the costliness, in human lives and suffering, of military expeditions undertaken in tropical climates, of armies rapidly dwindling in numbers and losing their effective fighting power quite apart from the infliction of battle casualties by the enemy. Such was the experience of Sennacherib, the Assyrian before Lachish, Alexander the Great in his conquest of Asia, the Spaniards in their conquest of the New World, the Dutch in the East Indies and the British in India. It is no wonder then that the tropics came to be feared as evil in themselves.

With advances in medical knowledge, it became clear that much of this morbidity could be attributed to specific diseases, more especially those loosely referred to as 'tropical diseases'—malaria, yellow fever, typhus fever, and the bowel disorders, typhoid, cholera and the dysenteries—but there still remained the firmly rooted conviction that there was a residuum of morbidity directly attributable to exposure to extremes of heat and humidity. Today this belief finds its expression in the practice of sending children 'home' from the tropics to be brought up, in the granting of generous leave in temperate climates to officials serving in the tropics, and in the short tours of duty assigned to troops in tropical areas. To this residuum of morbidity, i.e., that due to the influence of climate *per se*, the term 'tropical fatigue' has come to be applied.

The modern developments in the effective control of tropical disease, especially the outstanding work of Brigadier N. H. Fairley on malarial prophylaxis and treatment, has caused this so-called tropical fatigue to assume greater relative importance as a disability-producing factor in tropical warfare. The entry of Japan into the recent war and the engagement of Australian and Allied troops in the Southwest Pacific Area provided both the opportunity and the necessity for investigating the noninfective aspects of tropical disabilities.

About the middle of 1944, it was decided that an investigation into the nature and incidence of tropical fatigue among military personnel serving in the Southwest Pacific Area should be conducted under joint arrangements

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between the Australian Military Forces and the Royal Australian Air Force, and that facilities and personnel should be made available by both these organizations.

Such an investigation would have to establish two points; first, the existence of tropical fatigue; and second, its nature. With respect to this second point, it is obvious that if tropical fatigue exists, it may be either a physical or a mental phenomenon or a combination of both. Enquiry revealed that, in general, the methods available for the investigation of psychological phenomena are not suitable for a field survey. It was decided, therefore, to concentrate on the physiological aspects and to treat the mental aspects largely by a method of elimination.

The following approach to the problem was therefore adopted: *a*) to record the opinions of commanding and medical officers as to the efficiency of personnel in relation to length of tropical service; *b*) to measure by suitable tests the physical condition of personnel and to relate these measurements to the length of tropical service; *c*) to determine the extent to which tropical fatigue may be considered a psychological phenomenon by comparing the physical deterioration found with the loss of efficiency reported.

It was intended that this should be a preliminary survey and that any positive findings should be followed up by the continuous study of a unit actively engaged in warfare. The cessation of hostilities made this impossible.

#### METHODS

The method of investigation falls naturally into two divisions: *a*) the collection of data in the field and *b*) the analysis of such data. The question of what data to collect had to be answered on *a priori* grounds. It is obvious that any added strain of tropical living would have to be borne chiefly by the cardio-vascular, nervous and heat regulatory mechanisms, and this, to a large extent, determined what physical examinations would be made. During the course of the survey other factors—sickness rate, the nature and extent of weight changes, the prevalence of skin affections, the effect of glare—came to assume importance and subsidiary investigations dealing with them were conducted.

The collection of data in the field fell into three divisions: *a*) the taking of adequate histories; *b*) the conduct of the physical examination; and *c*) general observation and interrogation.

In the taking of the case history, each subject was first assigned a serial number and assured of anonymity. The date and place of examination were then entered, together with routine particulars such as rank, age, marital state, civilian occupation, date of enlistment and embarkation. A

careful location history involving the two years prior to the date of examination was then taken in order that the subject's climatic experience might be adequately assessed. His present and any previous musterings (i.e., service occupational grouping) were recorded, and enquiry was made as to whether he liked or disliked the duties assigned to him and why. Under the heading 'Incentives' was recorded an assessment, on a numerical basis, of

TABLE 1. CORRELATION BETWEEN HARVARD PACK TEST INDEX AND OTHER ITEMS IN TROPICAL PERSONNEL

ITEM	COEFFICIENT OF PARTIAL CORREL.	COEFFICIENT OF PARTIAL REGRESS
a) Significant at 0.1% level		
Subjective estimate of efficiency.....	+ .328	+6.44/unit*
Length of tropical service.....	- .187 - - .225†	-0.193 - - .242/wk‡
Intensity of mental work.....	+ .141	+2.59/unit*
Previous tropical exposure.....	- .116	-0.062/wk‡
b) Significant at 5% level		
Objective estimate of efficiency.....	+ .088	
Promotion incentive.....	+ .077	
Medical history during tour.....	- .063	
c) Not significant		
Unit incentive.....	+ .061	
Medical history prior to tour.....	- .060	
Intensity of physical work.....	- .055	
Duration of mental work.....	+ .035	
Duration of physical work.....	- .002	

\* Item estimated on a basis of 4 units from lowest to highest.

† Depending upon factors excluded in calculating partial correlation and regression.

‡ Per week of tropical as opposed to temperate exposure.

the factors, such as unit esprit de corps, expected promotion and relation to operational activities, considered conducive to maintenance of a high standard of efficiency. The man's habits with regard to alcohol and tobacco were recorded. The subject was then asked whether he considered that his efficiency as an airman and tradesman, and, in appropriate cases, as an NCO, had improved, deteriorated or remained stationary since his arrival in tropical areas. He was then further asked to assess his efficiency in terms of 'excellent', 'superior', 'satisfactory', 'moderate', 'inferior'. Later the subject's officer, or senior NCO, was asked the same question concerning each man. These two assessments are referred to as 'subjective estimate of efficiency' and 'objective estimate of efficiency', respectively. The type, intensity and duration of the work performed by the subject was then recorded and any special circumstances connected with his duties noted. Next a comprehensive medical history was taken and divided into two parts, the first dealing with the period prior to commencement of the current tour

and the second with that tour. Finally, any information concerning the man, volunteered by him or supplied by his medical or commanding officer, and considered to be of interest or importance was added.

For convenience in statistical analysis of the data provided, the results, where possible, were recorded according to a predetermined numerical scale.

The physical examination commenced with the assessment, according to the predetermined scale, of the subject's stance, gait, dress and complexion. The stability of the cardiovascular system was then examined by observing the reactions of the pulse rate and blood pressure to sudden elevation to 70° after twenty minutes' rest on a tilt table. The subject's sensations on tilting were also recorded. The height and weight (clothed and nude) having been determined and the time noted, the subject then underwent the Harvard Pack Test for the assessment of his cardiovascular reactions to acute maximal exercise.

In this test, as originally described by Johnson, Brouha and Darling (1), the subject wears a pack weighing one-third of his body weight and steps up onto and down from a platform sixteen inches high, once every two seconds, until he cannot maintain the pace or until five minutes have elapsed. The Index is given by the formula

$$I = \frac{100 \times \text{Duration in seconds}}{\text{Twice the sum of the pulse beat counted } 1-1\frac{1}{2}, 2-2\frac{1}{2}, 4-4\frac{1}{2} \text{ minutes after cessation.}}$$

At this stage, the wet and dry bulb and globe thermometer readings were recorded. After a rest period of 30 minutes, the subject was submitted to a subacute exercise test which consisted of marching in a standard dress, carrying a standard pack of 18 kilos, for 30 minutes at standard marching pace. At the conclusion of this test, his pulse rate was observed over a period of 30 minutes and his heart auscultated to ensure that no abnormality of heart sounds or rhythm had been uncovered by the exercise. The examination was concluded by weighing the subject again, both clothed and nude, and recording the time of the weighing.

The completed case sheets, which were recorded in duplicate, were checked and despatched with ancillary data for statistical analysis at the University.

## RESULTS

### *A. Harvard Pack Test Index*

From table 1 it will be seen that the subject's own estimate of his efficiency was fairly closely associated with his score. It will be seen also that, although the regression with length of tropical service is small, it would attain an important magnitude after one year. Previous tropical

exposure, on the other hand, has less than one third of the effect of tropical service.

Again, while the correlation between intensity of mental work and the index obtained is relatively low, the difference (10.36 units) between those engaged in the extremes of mental work may be quite important. The low rating of the driver-despatch rider group (table 2), as compared with other musterings, is noteworthy.

TABLE 2. DISTRIBUTION OF HARVARD PACK TEST INDEX WITH MUSTERINGS IN TROPICAL PERSONNEL

1. Driver-despatch rider group			
a) Significantly lower			
at 0.1% level	than in	Heavy skilled labor group.	
b) Significantly lower			
at 1% level	than in	Heavy unskilled labor group.	
c) Significantly lower			
at 5% level	than in	Light unskilled labor; Light skilled labor; Instructor and supervisor groups.	
2. Other groups			
No significant differences			

From table 3 it will be seen that, in general, those factors which were found to be correlated in a highly significant manner with the Harvard Pack Test Index in the tropical group are not significantly associated with it in the control group. This emphasizes the peculiar importance of these items in the tropics. The score obtained with this test by infantrymen was not affected by 4 to 9-day jungle patrols.

### *B. Other objective estimates*

Table 4 compares the results obtained for certain other objective estimates in the tropical and the control groups. It will be seen that, while there are differences between the groups which are highly significant statistically, the absolute value is small and not correlated with length of tropical service.

No progressive loss of weight was found in a group of 236 men of an AIF infantry battalion, except in those who had a high first weight. There were no important weight changes in infantrymen engaged on 4 to 9-day jungle patrols.

Beyond a slight and possibly significant fall in systolic blood pressure, and a slight increase in dizziness on tilting, there were no observable differences in cardiovascular function between the tropical and the control groups of RAAF ground crew; but a suggestion of slight residual increase in cardiovascular instability was found in the men returning from jungle patrols.

### C. Clinical findings

The comparative incidence of clinical disturbances in the tropical and the control groups of RAAF ground crew was  $1.218 \pm .039$  and  $0.992 \pm .063$ , respectively, as measured by a numerical assessment of the medical history given by the men. This difference is significant at the 0.25 per cent level.

TABLE 3. COMPARISON OF THE CORRELATION OF OTHER ITEMS WITH HARVARD PACK TEST INDEX IN TROPICAL AND CONTROL GROUPS

ITEM	LEVEL OF SIGNIF. IN TROPICAL GROUP	LEVEL OF SIGNIF. IN CONTROL GROUP
Subjective estimate of efficiency	0.1%	N.S.
Intensity of mental work	0.1%	N.S.
Previous tropical exposure	0.1%	N.S.
Objective estimate of efficiency	5%	N.S.
Promotion incentive	5%	N.S.
Medical history during tour	5%	0.1%
Unit incentive	N.S.	N.S.
Intensity of physical work	N.S.	5%
Duration of mental work	N.S.	N.S.
Duration of physical work	N.S.	N.S.

As regards the type of clinical disturbance in the tropical personnel examined, the following observations are pertinent: *a*) respiratory diseases were uncommon; *b*) the incidence of malaria was low and no man examined had had typhus; *c*) mild diarrhea was common, but dysentery rare; *d*) burns, usually minor, were quite frequent; *e*) functional disorders were common, in spite of the fact that no man examined had been a battle casualty; and *f*) skin affections were very common.

In those men considered to be showing a functional disorder, the following symptoms were usually complained of: sleeplessness, headache, vague abdominal pain, loss of appetite, pains in the back, supposed loss of weight and dizziness on standing up. Examination suggested that the symptoms resulted rather from an elevation of the significance of minor disturbances than from an increased frequency or intensity of the events themselves.

It early became evident that skin affections were prevalent in the tropical personnel and constituted both a source of annoyance to the men concerned and a threat to the effectiveness of the force. The extent of the affliction can be gauged from the fact that, in a random sample of 450 ground crew from our records, whose average length of tropical service was 31.7 weeks, 256 (57%) had developed one or more skin lesions. It was estimated that out of 100,000 man-days of service represented by this group of 450 men, a minimum of 800 man-days were completely noneffective and a



minimum of 9000 partially noneffective from this cause alone. The percentage incidence naturally rises with continued exposure, and it was estimated that, after twelve months' service in the areas concerned, the incidence of skin affection in the force would have attained a steady figure of about 80 per cent.

#### *D. Commanders' reports*

*RAAF.* All officers questioned stated quite definitely that deterioration occurred in the ground crew after a time, but they differed in their estimate of the length of time and the degree of failure involved. It was generally agreed that men were relatively inefficient for two or three weeks

TABLE 4. COMPARISON OF OTHER OBJECTIVE ESTIMATES OBTAINED IN TROPICAL AND CONTROL GROUPS

ITEM	TROPICAL GROUP		CONTROL GROUP
	Mean & S.D. of mean	Correl. $\bar{c}$ length trop. serv.	Mean & S. D. of mean
Stance (arb. units).....	3.38 $\pm$ .027	-.013	3.96 $\pm$ .054
Gait (arb. units).....	3.37 $\pm$ .028	+.065	3.81 $\pm$ .050
Dress (arb. units).....	3.37 $\pm$ .031	-.005	3.86 $\pm$ .051
Nude weight (kilos).....	65.30 $\pm$ .231	+.028	67.58 $\pm$ .488
Height-weight ratio (cm/kilo).....	2.67 $\pm$ .007	-.013	2.37 $\pm$ .014

after arrival, but that after that they maintained a steady state of approximately normal efficiency for six months. Deterioration was thought to commence at varying periods thereafter and to be well marked by 12 months. There was a common belief that the length of the tropical tour of duty had been officially set at 15 months for ground crew. Most officers agreed that this belief had a lot to do with the time factor in the onset of deterioration.

The evidence for deterioration appeared to be threefold: *a*) increase in the time taken to perform a task; *b*) reduction in the quality and reliability of performance as revealed by inspection; and *c*) increased complaints in respect of minor disabilities and minor annoyances.

Factors which officers felt were conducive to more rapid and marked deterioration included setting a time limit to tropical service; too much heavy work; too little and boring work; separation from the family; reports of misbehavior by the family; sexual deprivation; a feeling that reliefs were unduly delayed en route; a feeling that the particular work being done was unimportant or even futile; prior service in areas with hot climates which did not, however, count towards the period of tropical service; absence of rest areas in contact with civilized communities; and association with other groups (fighter pilots) who had very much shorter periods of tropical service.

*AMF.* Army medical officers gave the general impression that they considered complaints of tropical fatigue largely exaggerated. They emphasized the important effect of constant activity (within reasonable limits) and the possession of objectives clearly apparent to the individual soldier.

Some commanding officers felt that the Australian public was responsible for a part of any reduction in general efficiency which might exist: first, because they did not give the impression of being actively concerned in a total war effort (in contrast to the people of England) and second, because too much emphasis was placed by some members of the public upon the comfort and entitlements of the soldier engaged in active operations. War, it was pointed out, is a grim business, and a man who is being constantly reminded of what he is missing and what he is entitled to is less likely to become inured to its inevitable hardships. Leave, in particular, it was considered, would best come as a reward for work done, and in accordance with operational requirements, not as an automatic entitlement with the effluxion of time.

#### *E. Subjective estimates*

Almost every one of the tropical RAAF ground crew examined asserted in general conversation that he was not personally as efficient as when he entered the tropics. When later interrogated more exactly, however, as to whether he considered his standard of efficiency as an airman and a tradesman had improved, remained stationary or deteriorated, he gave a somewhat brighter picture. The results given by this later interrogation still show a distinct contrast, however, with the replies obtained in a similar way from the control group, as indicated by the following table:

#### *Percentage of Replies*

	<i>Tropical</i>	<i>Control</i>
Improved	11	65
Stationary	55	29
Deteriorated.	33	5

When further questioned as to what changes they had noticed, and from what disabilities they had suffered, the tropical personnel complained of one or more of the following: loss of weight, loss of energy and a feeling of constant tiredness, inability to produce their customary amount of work in the tropics, increase in ill-health, a feeling of general malaise, a loss of appetite, unreliable memory, loss of initiative, slowing of the mental processes, and increased irritability. The relationship between these subjective experiences and the complaints of those who had developed frank psychological insufficiency (3c) will be evident.

No comparable systematic interrogation was conducted upon members of the AMF, but we can state quite definitely that the individual soldier was not nearly so conscious of deterioration and loss of efficiency.

#### *F. Qualitative observations*

In common with other scientists, we prefer to deal with carefully collected quantitative measurements, but the qualitative impressions of a trained observer sometimes make available evidence which could not have been obtained in any other way under the circumstances prevailing. We believe that certain observations we made and opinions we formed are of this nature.

There appeared to have been little, if any, indoctrination of the men as to the effect they might expect the tropical climate to have *per se* upon their physical and mental well-being. It is doubtful if this was properly understood, even by senior officers.- In this respect, the AMF had gained some advantage through its experience in the Middle East, but the effects of a humid tropical climate are often quite different from those of a hot arid climate.

In many instances no forethought appeared to have been given to the protection of men and their working places from the worst climatic effects. Bush shelters, awnings and tarpaulins are easily rigged but were frequently neglected on the score that it was 'not the unit's job'. In the absence of unit instructions, the men seldom took appropriate action on their own account. White coral in the working areas is easily covered with darker soil mixed with a little oil, but this was often neglected and the discomfort from glare was allowed to persist.

Evidence of loss of efficiency seemed to occur particularly where one or more of the following conditions existed: human material of less than average quality; poor unit spirit and lack of esprit de corps; lack of tasks of obvious operational significance; insufficient man-mastership and discipline; inadequate organization of leisure time; monotonous diet, bad cooking and poor eating conditions; the siesta habit; and indiscriminate medication privately or from the medical supplies.

Where the following practices operated, they appeared to favor the onset of deterioration or to make more evident the psychological consequences thereof: establishment of a set period as the tour of tropical duty; differentiations in the rate of pay for a given rank, so that a markedly junior rank might be better paid than a senior rank charged with discipline; promotion within the service instead of within the command; absence of rest areas within the combat zone in which relatively normal civilization might be encountered; and inadequate selection of personnel in relation to the duties to be performed.

## DISCUSSION

*Existence of deterioration*

There is no doubt that in the light of the evidence given there was a lowering of general efficiency in the RAAF ground crew surveyed in the tropical areas, as compared with those examined near Brisbane. A comparable systematic survey was not made of members of the AMF, but close contact with that service led us to believe that deterioration was much less marked in them, except perhaps in the case of skin affection.

*Nature of the deterioration*

Beyond a slight initial loss of weight and a doubtful increase in vasomotor instability, the only evidence of any deterioration in what might generally be termed 'physical fitness' that we were able to obtain by objective examination was that given by the Harvard Pack Test Index, which showed a net fall of 0.19 units per week of tropical service. While small, this regression may represent an important deterioration after 12 months or more of tropical service. It is noteworthy, too, that this index was significantly affected in tropical personnel by the subject's own estimate of efficiency and by previous tropical exposure but unaffected by these factors in the control personnel.

On the other hand, the extensive incidence of skin affections must be taken as evidence of deterioration of a physical order, if only because of the actual or potential handicap it presents to the efficient conduct of the man's duties. It should, however, be considered in a different category from that of a general reduction in physical fitness.

Even when due allowance is made for the extensive incidence of skin affections, it is evident that the degree of physical deterioration found is totally inadequate to account for the marked loss of general efficiency apparent in the ground crew. The fact that AMF personnel, exposed to a physical environment which is no better, show less marked loss of efficiency also suggests that the physical aspect plays a lesser rôle in the production of this deterioration.

We are left, therefore, with the conclusion that a major part of such deterioration as does occur is of a psychological order. We realize, of course, that physical and psychological factors, whether as causes or effects, cannot be entirely dissociated, but we do feel that the evidence undoubtedly calls for the emphasis to be placed upon the psychological.

This conclusion, first formulated by comparing the physical deterioration found with the total inefficiency complained of, is amply supported by the other evidence collected concerning RAAF ground crew. To recapitulate, the high incidence of functional disorders, the reduced subjective appreciation of efficiency, the frequent complaints of vague subjective

were made and recorded of objective indices such as stance, gait and dress, height and weight, circulatory reactions to tilting, rate of sweat loss and evaporation, Harvard pack test, subacute exercise test. Correlation of objective indices with length of tropical service and other items was sought statistically and, where they were significant, regressions determined.

Subsidiary investigations were made of weight loss, skin disease, surface brightness and the effect of jungle patrols.

The main facts emerging from a statistical analysis of the data obtained were a) the Harvard Pack Test Index in tropical personnel showed the following associations: a reduction of 0.06 units per week of previous tropical exposure; a reduction of 0.18 units per week of tropical service; a rise with the intensity of the mental work customarily performed; a close association with the subject's own estimate of his efficiency; and a significant reduction in the driver-despatch rider group. b) Only a slight increase in vasomotor instability was discernible in tropical personnel. Pulse rates and blood pressures were relatively unaffected. c) While tropical personnel showed slight losses of weight as compared with controls, there was no evidence that this was progressive. d) Fifty-seven per cent of personnel (average tropical service 31.7 weeks) had contracted some skin disease, although usually of mild or moderate degree. e) As against the relatively slight objective findings, there was no doubt that reduced efficiency was wide-spread in RAAF ground crew. This was revealed by officers' replies to questions, lowered subjective estimates of efficiency, undue complaint by the men of minor affections and increased attendance for medical attention.

While climatic effects *per se* can be cited as the major cause of skin affections and a contributory cause of general inefficiency, the observers were led to the conclusion that personal and psychological factors were of paramount importance, and that much of the inefficiency is preventible by realistic handling of these factors.

The authors wish to acknowledge the encouragement and very ready help they received from the Directorate of Research, Allied Land Headquarters; the Director-General of Medical Services, RAAF, and the Flying Personnel Research Committee; and from all officers of the field forces investigated. Invaluable guidance was given in the statistical work by Squadron Leader McGovern. Without the willing assistance of the RAAF members of the Tropical Research Party and the AWAS attached to the Physiology Department, the extensive and often monotonous work could not have been carried through.

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*Observations on a Mobile Arctic Force.<sup>1</sup> The Health,  
Physical Fitness and Nutrition of Exercise  
"Musk Ox", February-May 1945*

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THE EFFECT ON MAN of the stresses and strains of Arctic travel in North America has never been studied systematically by means of modern physiological techniques. The Canadian Army Exercise 'Musk Ox' afforded an opportunity to carry out such a study. The objectives of the exercise were to send a mechanized force across 3400 miles of the Arctic in midwinter to determine the effects of environmental stresses on vehicles, equipment and personnel, and to collect scientific data on the Canadian northland. Starting in February from Churchill on Hudson's Bay the 48 men of the moving force travelled in tracked snowmobiles northward to Queen Victoria Land. Here they turned west to Coppermine and moving south along the Mackenzie River basin reached Edmonton in May, with an itinerary shown in table 1 and figure 1.

All supplies for the moving force were dropped from aircraft of the Royal Canadian Air Force. The basic ration was the Canadian Army Arctic Field Service Ration Scale which provides a variety of perishable and

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non-perishable items in a daily issue of about 5000 calories per man. There were also periodic issues of U. S. Army Ration (10-in-1) and Canadian Army Monopack Ration (Arctic), both of which are packaged rations providing a variety of cereals, beverages, meat items, confections and biscuits. It was planned to issue Canadian Interservice Vitamin Capsules if an emergency arose, but at Eskimo Point the whole supply was inadvertently lost.

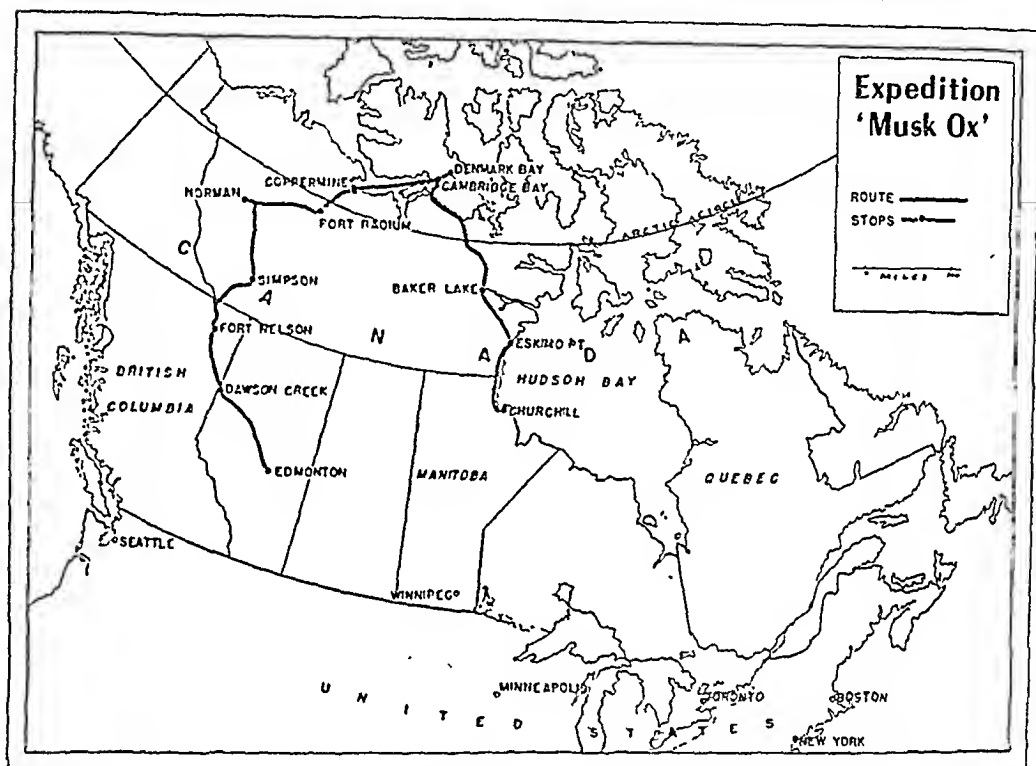


Fig. 1. MAP OF ROUTE TAKEN BY MOVING FORCE, Operation 'Musk-Ox', Canadian Army, from Churchill, Manitoba (14 Feb. 1946) to Denmark Bay, Queen Victoria Land (20 Mar. 1946), and to Fort Nelson, British Columbia (29 Apr. 1946).

Water was obtained throughout most of the journey by melting ice or snow, and the bulk of the fluid intake was in the form of soups, coffee, tea and other beverages.

#### METHODS

The troops for the operation were selected after a thorough medical examination and commenced training at Camp Shilo, Manitoba, in November 1945. Their general medical care was in the hands of three medical officers (R. R. M. C., R. M. M. and A. B.), one of whom (R. R. M. C.) travelled with them throughout the whole journey. A special medical board examined the men and measured their physical fitness (7, 11) and biochemical status with the aid of an air-borne mobile laboratory (13). The observations were made at Churchill on Hudson's Bay in February and repeated at Fort Nelson in northern British Columbia in May.

Estimates of food consumption and wastage were made from records of food supplied and from dietary histories taken from the men (3, 5).

All data were analyzed statistically. Standard errors of the differences of means were calculated and then the significance ratios, differences of the means divided by the standard errors of the differences of the means. From tables of areas of the normal distribution curves, probabilities were calculated. For samples in which the number of observations were less than 30, 't' tables were employed to include a correction for small numbers of degrees of freedom. Throughout this paper a difference is considered statistically significant if the probability is less than 1 in 20 that the difference could occur by chance.

TABLE 1. ITINERARY OF EXERCISE 'MUSK OX'

DATE	PLACE	MILES FROM CHURCHILL	LATITUDE	LONGITUDE	MINIMUM TEMP.
			°N	°W.	°F.
14 Feb 1946	Churchill, Manitoba	0	59	94	-40
21 Feb 1946	Eskimo Point <sup>1</sup>	209	61	95	-48
2 Mar 1946.	Baker Lake <sup>1</sup>	489	64	96	-26
13 Mar. 1946	Perry River <sup>1</sup>	809	67	101	-9
15 Mar 1946	Cambridge Bay <sup>1</sup> (Queen Victoria Land)	963	69	104	-10
20 Mar. 1946	Denmark Bay (Queen Victoria Land)	1070	71	103	-41
28 Mar 1946	Coppermine <sup>1</sup>	1493	67	115	-28
5 Apr. 1946	Port Radium <sup>1</sup>	1666	66	118	-10
12 Apr. 1946	Fort Norman <sup>1</sup>	1918	65	125	+4
20 Apr. 1946	Fort Simpson <sup>1</sup>	2289	62	120	+33
29 Apr. 1946	Fort Nelson, B. C.	2496	59	123	+38
4 May 1946	Fort St John, B. C.	2921	55	118	+39
6 May 1946	Edmonton, Alberta	3328	53	114	+35

<sup>1</sup> Points of stop-overs

## RESULTS

### *General description of environment*

During the first two thirds of the journey the weather was very cold and windy, with occasional severe blizzards. In one period of two weeks the temperature never rose above 28°F. Once the tree belt was reached at Great Bear Lake, near Port Radium, progressively milder conditions were encountered: and the spring breakup was in progress when the force reached Fort Nelson.

There were four men in the crew of each vehicle, operating as a more or less independent unit responsible for maintaining its own camp site, cooking and preparation of food and the maintenance of the snowmobile. The whole force was organized as three divisions of five or six vehicles each, which operated separately. Radio contact was maintained among the three divisions. When the force was moving, a typical day began at any time of the morning from 0300 hours on, depending upon prevailing and anticipated



conditions. After preparing breakfast and warm beverages for noon and breaking camp, they started the day's journey over virtually uninhabited territory. During the day there was usually one short break of about half an hour for a meal, consisting of previously prepared warm fluids contained in thermos bottles, and cold or warm items of food from packaged rations. After the noon halt, driving was continued until the night camp was established. On arrival at the day's destination some three or more hours were spent setting up camp, preparing the evening meal, maintaining the vehicle and performing other duties. This typical day's schedule was modified by

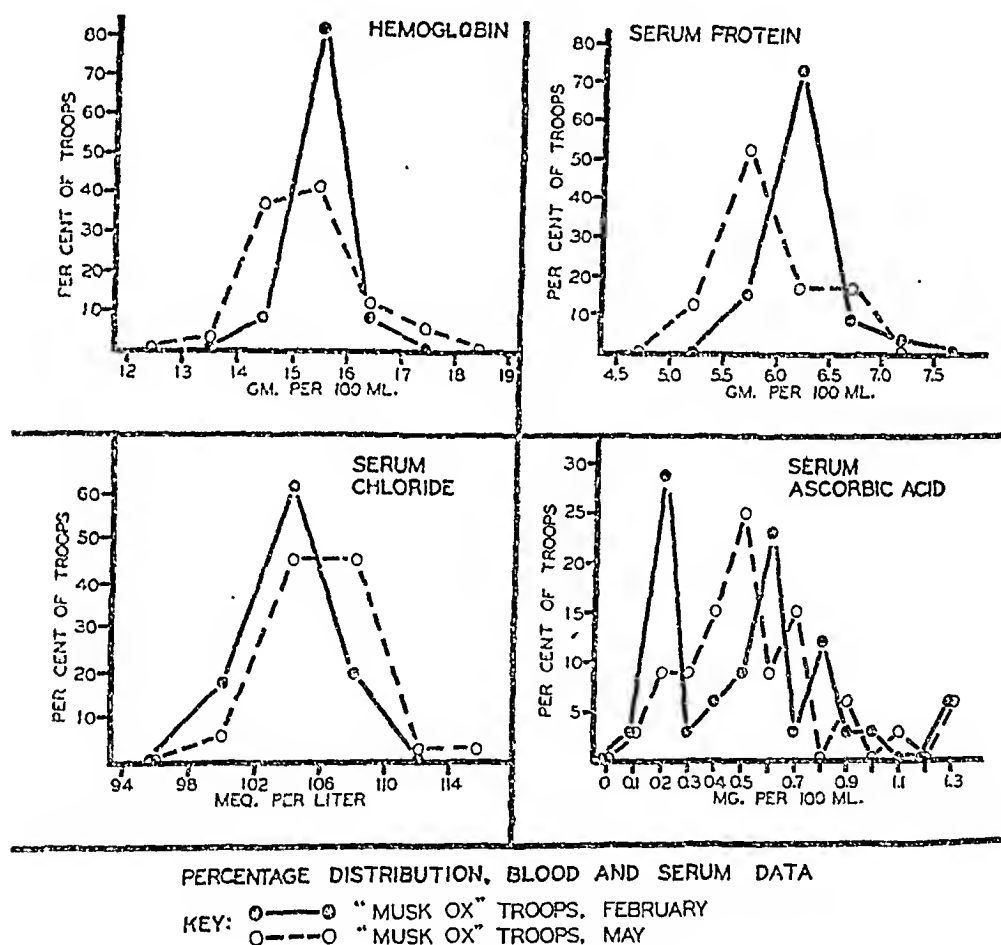


Fig. 2. PERCENTAGE DISTRIBUTION CURVES for data on hemoglobin, serum protein, serum chloride and serum ascorbic acid for 'Musk Ox' troops, at Churchill, Manitoba (Feb. 1946), and at Fort Nelson, British Columbia (May 1946).

inclement weather, bad terrain and mechanical trouble. Over the whole journey the average daily distance covered was about fifty miles.

The men were clothed typically in soft flannel pyjamas, woolen underwear, at least two pair of heavy woolen socks, a woolen shirt, Canadian woolen battle dress, footgear consisting of mukluks, shoe pacs or felt boots (depending on weather conditions and personal preference) and, when

needed, outer protective garments consisting of a parka, windproof trousers, mitts, mufflers, face masks and goggles. The effectiveness of the clothing is attested by the complete absence of major frostbite, and a negligible incidence of minor frostbite of the extremities, ears, nose and face, among the men.

While they were on the move protection was offered most of the time by the closed cabin of the vehicle, which kept off the wind and in which the temperature rarely fell lower than  $0^{\circ}\text{F}$ . In camp, six-man, pyramidal double-walled, nylon, water repellent, nylon-floored Canadian Army Arctic tents were employed as sleeping quarters and the men bedded down in Army

TABLE 2. NUTRIENTS SUPPLIED TO EXERCISE 'MUSK OX' AND CALCULATED DAILY AVERAGE INTAKE AS COMPARED WITH THAT OF U. S. GROUND TROOPS IN TEMPERATE AREAS

NUTRIENT	TOTAL AMOUNT SUPPLIED	CALCULATED INTAKE	
		Exercise 'Musk Ox'	U. S. Ground Troops <sup>1</sup>
Daily average per man			
Water, liters . . . . .	—	1.2	—
Calories . . . . .	5190	4400 <sup>2</sup>	3790
Protein, total, gm. . . . .	145	120	125
Protein, animal, gm. . . . .	87	70	—
Carbohydrate, gm. . . . .	575	520	408
Fat, gm. . . . .	225	190	178
Rum, gm. . . . .	60	60	—
Vitamin A, IU . . . . .	6100	4900	12,000
Thiamine, mgm. . . . .	2.8	2.2	2.1
Riboflavin, mgm. . . . .	3.5	2.8	2.3
Niacin, mgm. . . . .	31	26	23
Ascorbic acid, mgm. . . . .	80	50	74

<sup>1</sup> From Howe and Berryman (10) for 455 messes in U. S. training camps 1941-1943.

<sup>2</sup> Including 280 cal. from rum.

Arctic sleeping bags. On a few occasions the men slept in igloos, but they much preferred their tents to igloos on the score of both warmth and comfort. On other occasions they slept in wooden buildings at white settlements. Gasoline stoves were used for cooking, melting ice and snow, and for heating the tents.

Personal hygiene was necessarily primitive. Owing to the scarcity of water, washing was infrequent and oral hygiene was neglected. Disposal of waste and excreta was not difficult and was safe because of the mobility of the force and the cold weather.

### *Physiological stresses of the environment*

Inspection of the manner in which the journey was organized will show that the troops were exposed to a variety of stresses and hazards. They

had to face cold, wind and solar radiation. In the vehicles they had to face fumes from the engines and heaters, jolting and abrupt movement, noise, discomfort from cramped quarters, low temperatures, glare and hazards such as burns and frostbite of the hands. With regard to rations, supply was always successful but preparing hot meals from frozen stores was always a problem. Water was difficult to obtain in adequate quantities and thirst was common. Adherence to an onerous schedule led to short hours of rest and a feeling among some of pressure. The troops had to face the psychological difficulties of danger, isolation and complete dependence on the air force for supply. The possibility of an unseasonable early spring breakup was a mental hazard toward the end of the journey.

TABLE 3. CALORIC CONSUMPTION AND RATIO OF PROTEIN, FAT AND CARBOHYDRATE EATEN BY VARIOUS BODIES OF GROUND TROOPS IN DIFFERENT ENVIRONMENTS

PLACE AND TROOPS	ENVIRONMENT	CALORIES CONSUMED, DAILY AV/MAN	PERCENTAGE OF CALORIES PROVIDED BY		
			Pro- tein	Fat	Carbo- hydrate
Canada, 'Musk Ox' . . . . .	Arctic	4400	11	40	49
U. S. Training Camps . . . . .	Temperate	3800	13	43	44
Colorado Rockies, Infantry Btn . . . . .	Mountain	3900	13	34	53
Luzon, 38th Infantry Division . . . . .	Wet Tropics	3200	12	34	54
Pacific Islands . . . . .	Wet Tropics	3400	13	33	54

### *Medical history and dietary history*

In all, 25 men were interviewed, 90 per cent of whom had travelled by snowmobile all the way through the barren lands from Churchill. Ten per cent of the men joined the force at Baker Lake and 5 men were flown forward from Coppermine to the subarctic forest region to improve the trail between Norman Wells and Fort Nelson. About 30 per cent of the men interviewed had been travelling in 'trail-breaking' vehicles or had been doing other very heavy work, such as bridge building.

Work done on the journey consisted mainly of driving, maintenance on vehicles, preparing meals, making and breaking camp and collecting supplies dropped by the air force. On the last leg of the journey trees and bushes had to be cleared from the trail and bridges and rafts were built. Usually the drivers averaged between 5 and 8 hours of active driving a day and observers, radio operators and crew leaders between 2 and 5 hours a day. Maintenance occupied 2 to 2½ hours, and cooking, melting ice and snow and eating took 3 hours or longer. At the beginning it took approximately 3 hours to make camp but this time was reduced considerably during the latter stages of the journey. The men slept about 6 to 7 hours a day and about 1

hour was spent in toilet. A typical day for a driver mechanic would be 6 hours driving,  $2\frac{1}{2}$  hours maintenance,  $1\frac{1}{2}$  hours eating, 2 hours making camp, 1 hour toilet, 4 hours as passenger or doing other jobs, and 7 hours sleep.

The force halted at eight places for periods of two to seven days (table 1) to make major repairs and to replace clothing and equipment. During such times regular hours of rest, relative comfort and unhurried meals, prepared indoors, were in marked contrast to the irregular hours, discomfort and strain of the journey. At points of layover the men were guests of the local inhabitants, although they provided their own victuals.

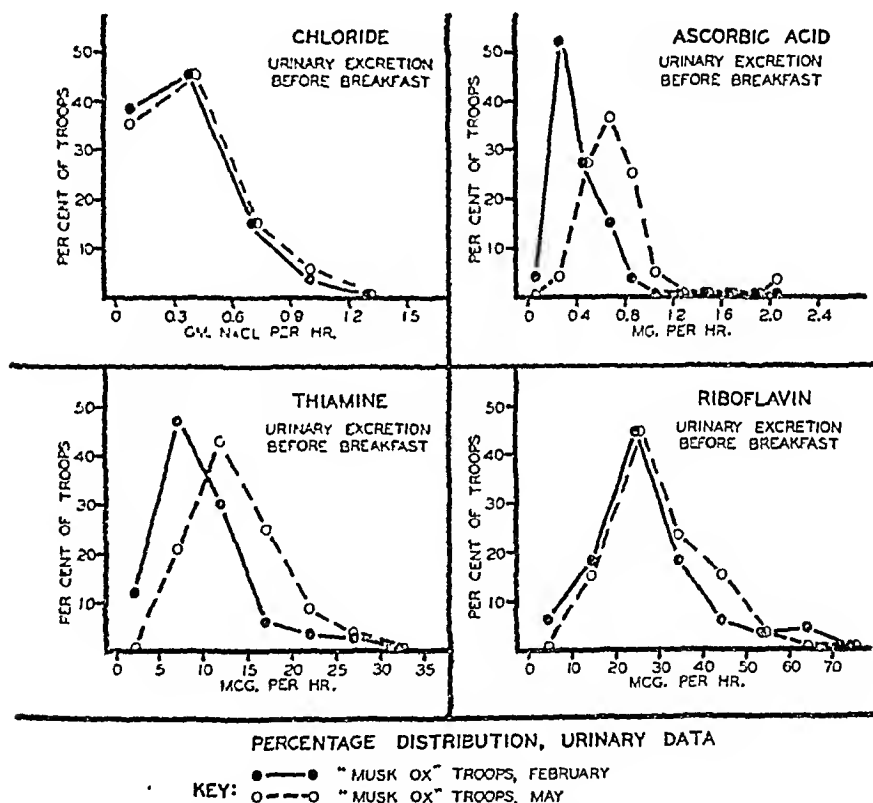


Fig. 3. PERCENTAGE DISTRIBUTION CURVES for data on chloride, ascorbic acid, thiamine and riboflavin excretion in samples of urine collected before breakfast from 'Musk Ox' troops at Churchill, Manitoba (Feb. 1946), and at Fort Nelson, British Columbia (May 1946).

There was very little illness. Three quarters of the force complained of symptoms which were attributed to carbon monoxide poisoning. About 65 per cent of the force had severe symptoms near Baker Lake, as a result of inhaling exhaust gases blown back into the vehicles by a strong following wind, and some of the men collapsed. After this episode 30 per cent of the men had headaches and other mild symptoms on occasion.

The men suffered few ill effects from the cold, with an incidence of only 10 per cent with minor frost bite of the face or fingers. Eighteen per cent had single attacks of mild upper respiratory infection, 20 per cent had very slight gastro-intestinal upsets such as nausea, diarrhea, and constipation. Three men noticed a change in urinary function with frequency by night and day. Injuries were negligible. Ill effects from glare were not reported by anybody.

Many of the men became irritable toward the end of the journey. The factors contributing to this state of mind were stated to have been lack of sleep, strain of trying to finish the journey on schedule, monotonous engine noise, fatigue caused by the jolting of the vehicle and thirst. When the weather was bad, with severe cold, high wind and poor visibility, the men were depressed and confinement to the vehicles was particularly onerous, but, generally, physical factors encountered were compensated for by adequate clothing and food and equipment, and on clear bright days spirits were good. Fear was mostly in anticipation of danger but some of the men were very touchy when crossing lake or river ice.

During the journey each man had a good appetite. This was satisfied except in about 16 per cent of the men who complained that they did not get quite enough to eat, as the time factor did not permit them to prepare all the food they wanted. These men, on the average, lost more weight than their companions. One man complained that the food supplied did not provide enough 'bulk'. Sixty per cent of the men said that their daily intake of food was greater than the daily intake of food during their early winter training at Camp Shilo, Manitoba, where they lived on the Standard Canadian Army Ration (Garrison Ration) supplemented by food bought in restaurants or canteens (post-exchange).

#### *Food intake, wastage and caloric balance*

During the training period at Churchill prior to the journey, the moving force fed with base personnel at an army mess. The Canadian Army Arctic Field Service Ration Scale was used. Food consumption was large because of several factors: daily work was arduous and conducted under bitter cold conditions; appetites were excellent; training policy encouraged putting on body weight in preparation for the journey to come; supply of food was ample and the cooks were good. Organization was such that exact estimation of food consumption was impossible. For instance, it is known that two thirds of the men voluntarily took at least one vitamin pill every other day. The best estimate we can make gives the following orders of magnitude as the maximum daily average per man: 5000 calories, 11,000 IU vitamin A; thiamin 3 mgm.; riboflavin 5 mgm.; niacin 35 mgm.; and ascorbic acid 90 mgm.

During a period of 78 days on the journey the men received 27 days' supply of fresh rations, 39 days' supply of U. S. Army Ration 10-in-1 and 12 days' supply of Canadian Army Monopack Ration (Arctic). In addition there was a daily rum ration and on a few occasions the force had access to small quantities of doughnuts, precooked pork and beans, fresh caribou meat, ptarmigan, U. S. Army C and K rations and extra supplies of bread and fruit juices.

Table 2 shows the nutrient content of the foodstuffs actually supplied the troops and the average daily nutrient intake per man for the whole duration of the trip. These values are calculated from records of food dropped, from estimates of wastage in dropping and in preparation, and from interviews with the troops. The procedure of Berryman and colleagues (3-5) has been followed for computing nutrient intake.

Generally speaking there was little wastage. Various competent observers among the force estimated that from 10 to 15 per cent of the 'raw' rations and less than 5 per cent of the cooked food was wasted. In packaged rations major wastages were of biscuits (50 to 70%); cheese items (50 to 90%); pork and apple (25 to 50%); ham and raisin (50 to 70%); 10-in-1 lunch units (25% of total); and granulated sugar and cocoa.

On a caloric intake of 4400 calories per day (table 2), caloric balance was well maintained when judged by maintenance of body weight, as will be discussed later. The estimates of caloric intake were checked in two ways. First, from the 5480 calories supplied on days when fresh rations were issued, the average daily consumption was 4480 calories. Second, when the men were living on the packaged 10-in-1 ration, four men shared 21,000 calories a day and of this wasted 4700 calories, mostly in the biscuits, with a net consumption of 4100 calories per man per day. In addition to this 4100 calories from the packaged ration, each man obtained a further 300 calories per day from the rum ration and other minor sources of food, such as doughnuts.

Table 3 shows that the overall average caloric intake of 4400 per man per day for 'Musk Ox' troops is somewhat less than the 4800 that has been reported for infantry troops in subarctic conditions (14, 18), is somewhat more than the 3800 reported for U. S. ground troops under temperate conditions (10) and is considerably higher than the 3400 reported for U. S. ground troops in the tropics (15). This table also shows that regardless of environment North American troops voluntarily consume about the same proportion of protein from their rations. There is no support in the table for the concept that troops living in the winter in the Arctic voluntarily consume a higher proportion of fat than in temperate conditions. Consumption of fat by U. S. troops in all environments, however, is much higher than the 25 to 30 per cent of calories from fat which is the figure usually

given in text books, and which pertain to normal civilian diets in temperate climates.

The troops of 'Musk Ox' voluntarily consumed on the journey protein, fat, thiamine and niacin in about the same amount as U. S. ground troops in training in temperate climates (table 3); they consumed more carbohydrate and riboflavin and less vitamin A and ascorbic acid. They did not receive enough vitamin pills to affect significantly their average daily intake of vitamins over the whole maneuver.

TABLE 4. PHYSICAL EXAMINATION OF 32 MEMBERS OF EXERCISE 'MUSK OX' AT THE BEGINNING AND NEAR THE END OF THE JOURNEY

FINDING	PERCENTAGE OF TROOPS WITH FINDING		
	Churchill, 12 Feb.	Fort Nelson, 1 May	Difference
<b>A. Eyes</b>			
1. Obvious corneal vascularization.....	12	15	+3
2. Conjunctivitis.....	18	30	+12
3. Gross changes, opacity of sclera.....	9	15	+6
4. Pingueculae.....	18	18	0
<b>B. Skin</b>			
1. Acneform eruption.....	3	6	+3
2. Folliculosis.....	67	83	+16
3. Infected folliculosis.....	0	12	+12 <sup>1</sup>
<b>C. Lips and mouth</b>			
1. Angular fissure.....	3	9	+6
2. Cheilosis.....	6	24	+18 <sup>1</sup>
3. Oral hygiene good.....	36	12	-24 <sup>1</sup>
Oral hygiene fair.....	58	61	+3
Oral hygiene poor.....	6	27	+21 <sup>1</sup>
4. Acute inflammation, dental margin.....	0	3	+3

<sup>1</sup> The odds are at the most 1 in 20 that these differences would occur by chance.

The most popular foods were fresh caribou meat (which was eaten at Baker Lake, Coppermine, Port Radium and Fort Norman), canned puddings, fruit and fruit juices, bacon, corn, candies, cereals and bread. The least acceptable foods were biscuits, three canned items, viz., canned ham with raisin, pork with apple, chopped ham with eggs, and cheese products.

There was no particular craving for fatty foods. Half the men stated that they ate more fatty foods, such as butter, than usual, but the other half either noticed an increased consumption of high carbohydrate foods such as porridge, candies, and jam, or no change. Those who ate more carbohydrate also stated that they were eating less fresh meat, potatoes, vegetables, bread and milk than usual.

### *Water and thirst*

Fluids were obtained by melting ice and snow. This was supplemented by occasional issues of fruit juice, soup (including soup in self-heating cans), evaporated milk and juices obtained from canned vegetables and fruit.

The average consumption of all fluids amounted to about 1.2 liters per day and was stated to have ranged from 0.7 to 3.4 liters. On this intake 75 per cent of the men complained of unsatisfied thirst due to the difficulty of obtaining enough water by melting snow and ice for drinking and making beverages. We have observed this previously in troops working in the cold who became dehydrated and excessively thirsty due to failure to get enough fluid from snow. Many men complained that the saltiness of the bacon (10-in-1 canned bacon) increased their thirst and they felt that the 'spiciness' of some of the canned meat components was also a factor which increased thirst. Thirst was a factor which influenced the palatability and acceptability of the different ration items eaten and which colored thought when the men indicated what food items they felt would be desirable for use in a future Arctic expedition. For example, canned fruits and fruit juices, canned vegetables and soups in self-heating cans were prominent among the items desired in larger amounts. They also felt that 'spiced meats' and salty food should not be included in an Arctic ration.

### *Physical examination*

When examined at the beginning and near the end of the journey the troops were healthy. No evidences were found of specific nutritional disease syndromes such as scurvy, nor of other gross abnormalities. During the journey there was an increase in the incidence of certain lesions, some of which are commonly attributed to nutritional deficiency (1). Table 4 shows the incidence of these lesions, which were: corneal vascularization detectable with a magnifying glass; gross increase in the opacity of the sclera; one single case of acute inflammation of the dental margins; angular fissures; cheilosis; acneform eruptions of the back and face; folliculosis, without or with superimposed infection, usually found on the buttocks, on the anterior and posterior surfaces of the thighs and calves and on the extensor surfaces of the upper arms. The lesions consisted of papules, involving the hair follicles. Sometimes the hairs were broken off and hyperkeratotic plugs filled and protruded from the follicles. When infected they became pustular. The great majority of the lesions noted were mild in degree and none was severe. No abnormalities of the neuromuscular system were detected.

In view of the data presented above on nutrient intake and of the biochemical findings presented below it seems reasonable to relate the presence



of the above lesions to environmental trauma rather than to specific vitamin deficiencies. The lesions of the eyes might well be attributed to exposure to wind, fumes from stoves and vehicles, lack of sleep and exposure to the bright sunlight. The skin lesions observed among the 'Musk Ox' troops are not common among Canadian soldiers living in temperate environments while receiving rations similar to those issued to the 'Musk Ox' troops (16).

TABLE 5. SUMMARY OF DETERMINATIONS ON THE BLOOD, SERUM AND URINE OF 34 MEMBERS OF EXERCISE 'MUSK OX' AT THE BEGINNING AND NEAR THE END OF THE JOURNEY

DETERMINATION	AVERAGE VALUE		
	At Churchill, 12 Feb.	At Fort Nelson, 1 Mar.	Difference
Hemoglobin, gm/100 ml.....	15.4	15.2	-0.2
Serum chloride, mEq/liter.....	103	106	+3 <sup>1</sup>
Urine chloride, gm. NaCl/hour.....	0.4	0.4	0
Serum protein, total, gm/100 ml.			
Copper sulfate method.....	6.2	5.9	-0.3 <sup>1</sup>
Kjeldahl method.....	7.2	7.0	-0.2 <sup>1</sup>
Serum albumin, gm/100 ml.....	5.0	4.7	-0.3 <sup>1</sup>
Serum globulin, gm/100 ml.....	2.2	2.3	+0.1
Serum nonprotein nitrogen, mgm/100 ml.....	33	33	0
Ratio, albumin/globulin.....	2.4	2.1	-0.3 <sup>1</sup>
Urine volume, ml. hour, before breakfast.....	51	53	+2
Serum ascorbic acid, mgm/100 ml.....	0.53	0.56	0.03
Urine ascorbic acid, mgm/hour, before breakfast.....	0.4	0.7	+0.3 <sup>1</sup>
Urine thiamine, mcg./hour before breakfast.....	9	13	+4 <sup>1</sup>
Urine riboflavin, mcg./hour before breakfast.....	27	29	+2
Urine N <sup>1</sup> -methylnicotinamide, mgm/hour before breakfast..	0.4	0.5	+0.1 <sup>1</sup>
Urine total nitrogen, mgm/hour before breakfast.....	390	637	+247 <sup>1</sup>
Urine creatinine, mgm/hour before breakfast.....	67	86	+19
Urine creatine, mgm/hour before breakfast.....	0	0.6	+0.6
Inorganic phosphorus, mgm/hour before breakfast.....	37	54	+17

<sup>1</sup> Statistical analysis shows that the probability is less than 1 in 20 that these differences could arise by chance.

The increased incidence and severity of folliculosis during the Arctic journey may be related to infrequent change of clothing, type of clothing, infrequent washing and chronic irritation from friction of the clothing during vehicular movement. Lesions of the lips might be associated with exposure to the elements. The decline in oral hygiene was due to the lack of opportunity to clean the teeth properly (18) among men accustomed to cleaning the teeth at least once daily.

On the average, body weight was well maintained. An average loss of three pounds per man in two and one half months was observed. This is of no statistical or nutritional significance. One obese 225-pound individual

(no. 41) lost 29 pounds in weight between Churchill and Fort Nelson. His past history includes several other occasions when his weight has fluctuated to this extent, depending on the balance between his food intake and muscular activity. When seen at Fort Nelson he was in excellent health. Data were obtained on the chest and abdominal circumference of 7 men. There was no statistically significant change in either measurement between Churchill and Fort Nelson. All of these measurements on body weight and size lend support to the conclusion that the men had a ration that was calorically adequate for their energy expenditure during this maneuver.

### *Tests of physical fitness*

Capacity for sustained hard muscular work was tested by means of the 'Pack Test'. At Churchill all members of the moving force were tested on successive days. The average scores of 76 and 78, respectively, compare favorably with those of well trained Canadian and U. S. troops studied elsewhere (15, 18). Eleven men were tested again at Fort Nelson. Their average score had increased from 80 to 85. Eight improved, one showed no change, one decreased two points and one decreased seven points. We conclude that the fitness of this group for muscular work was unimpaired by the stresses of the journey.

### *Biochemical results*

A summary of biochemical findings is presented in table 5, which gives average values for important constituents of the blood, serum and urine of 34 men who were examined both at the beginning and near the end of the journey.

a) *Hemoglobin.* Average values for hemoglobin in the blood showed no statistically significant changes during the expedition (fig. 2) and all values at both points of observation were well within the usual limits seen elsewhere in well nourished white troops (15). There is good evidence on clinical grounds that the men were exposed intermittently to toxic agents such as carbon monoxide and tetraethyl lead. Judging from the data for hemoglobin and microscopic examination of blood morphology at Fort Nelson, these toxic agents had not damaged the blood-forming organs or the circulating cells.

b) *Serum and Urinary Chlorides and Total Serum Protein* (fig. 2 and 3). All values for serum chloride were within normal limits both at Churchill and at Fort Nelson. However, there was a statistically significant average increase from 103 mEq/liter to 106 mEq/liter (table 5). At the same time there was no change in the rate of urinary excretion of chloride. These findings indicate that chloride balance was not disturbed and in addition

have a theoretical interest in view of a statistically significant decrease of 0.3 gram/100 ml. of total protein in the serum (table 5). When men who have been living in a cool environment for some time are exposed to a warm environment a process of acclimatization takes place. There are reports that this is accompanied by an increase in blood volume, with a slight increase in the concentration of serum chloride and a slight decrease in the concentration of serum protein. Bazett and colleagues (2) found increases in serum chloride and decreases in serum protein in the same direction and of the same order of magnitude as those seen in figures 2 and 3. It is probable that a process of acclimatization to heat was going on among 'Musk Ox' troops since the weather was very cold during the 50 days between Churchill and Fort Norman, whereas the troops worked hard in progressively milder weather during the 30 days between Fort Norman and Fort Nelson.

c) *Nonprotein Nitrogen, Total Protein, Albumin and Globulin of the Serum* (fig. 2 and 3). Nonprotein nitrogen in the serum was, on the average, within normal limits at the beginning and near the end of the journey, and there was no average change (table 5). Taken in conjunction with the negative findings reported below for routine urinalysis, these data indicate that kidney function was normal at both places of examination. Neither prolonged exposure to cold nor prolonged jolting throughout the trip had produced renal damage detectable by biochemical methods used here.

As measured by both the copper sulphate and the Kjeldahl methods the concentration of total protein in the serum was within usual limits for white troops (table 5). There was a difference between the absolute values obtained by the two methods. However, both showed statistically significant decreases of 0.3 and 0.2 gram/100 ml., respectively, between Churchill and Fort Nelson (table 5). This change was entirely accounted for by a decrease of 0.3 gram/100 ml. in the albumin fraction (table 5). The changes in the globulin fraction had no statistical significance (table 5). Possible causes for the slight decrease in concentration of the serum protein have been discussed above.

d) *Ascorbic Acid in Urine and Serum* (fig. 2 and 3). The average value for ascorbic acid in the serum did not change between Churchill and Fort Nelson (table 5) and in both instances was usual for troops in North America. This shows that the rations provided enough vitamin C to maintain as good a level throughout the trip as was present at the beginning. Those whose levels were at the lower end of the distribution curve for serum ascorbic acid at Churchill tended to show an increase by the time of reexamination two and one-half months later. Of 11 men examined whose values at Churchill were 0.2 mgm. per 100 ml. or lower, 8 showed an average increase of 0.4 mgm. per 100 ml. and the other 3 showed no change. This is

presumptive evidence that the troops found acceptable those items of food issued which contained vitamin C, and the dietary histories confirm this view.

The validity of comparisons of hourly rates of excretion of substances in the urine is affected by the rate of urine formation. If the hourly excretion of urine is less than 25 ml. results for certain vitamins tend to be abnormally low, whereas if the rate is over 150 ml. per hour there is for some substances a 'washing out' (12). In the present case comparisons are valid since the average excretion of urine in specimens collected before breakfast was 51 ml. per hour at Fort Nelson. The distribution curves show more variance at Churchill than at Fort Nelson but this dissimilarity was not statistically great enough to invalidate comparisons.

Urinary excretion of ascorbic acid averaged 0.4 mgm. per hour at Churchill and 0.7 mgm. per hour at Fort Nelson (table 5) and the difference of 0.3 mgm. per hour is statistically highly significant. At the same time the calculated intake of vitamin C was definitely higher at Churchill than during the expedition. The explanation for this lowered rate of excretion must remain speculative. However, in view of the data on intake of vitamin C, the lack of change in serum level of ascorbic acid and the constant urinary water output per hour, together with the absence of conditions usually related to a lowered rate of excretion of ascorbic acid, such as trauma and infection (9), a possibility exists that the change in excretion might be related to the extremely cold weather at Hudson Bay, as compared with the moderate temperatures encountered in northeastern British Columbia. This idea is possibly supported by the report that when exposed to a cold environment rats appear to store more vitamin C in the tissues and to excrete less in the urine than they do in a temperate environment (8).

*e) Urinary Excretion of Thiamin, Riboflavin and N<sup>1</sup>-Methylnicotinamide* (table 5 and fig. 2). At both points of observation the specimens were collected before breakfast. The rates of excretion of thiamine, riboflavin and N<sup>1</sup>-methylnicotinamide were all within limits usually found for healthy well nourished white troops.

For thiamine and N<sup>1</sup>-methylnicotinamide values were significantly higher at Fort Nelson than at Churchill, but there was no statistically significant difference in riboflavin excretion. Increases in the rate of excretion of N<sup>1</sup>-methylnicotinamide have been previously observed in hard-working troops in the cold.

It has been shown among troops in temperate and warm environments that there is a linear relation between the rates of excretion of thiamine and riboflavin and the average daily intake of these vitamins (15). The average values obtained at Fort Nelson fitted well with the data previously obtained.

*f) Urinary Nitrogen Partition and Inorganic Phosphorus.* Table 5 indicates that there was a definite increase in the fasting hour excretion of total

nitrogen at Fort Nelson over that found for the same subjects at Churchill. The creatinine excretion at Fort Nelson was increased but to a lesser degree. Four subjects showed slight creatinuria at Fort Nelson while none was demonstrated at Churchill. Slight increases in the excretion of inorganic phosphate were likewise found at Fort Nelson.

*g) Routine Urinalysis.* Qualitative tests for reducing substances, protein and ketone bodies were conducted at Churchill and again at Fort Nelson upon samples of urine from 34 men. Reducing substances were not present in any specimen. One subject showed slight proteinuria at Churchill but not at Fort Nelson. As judged by the Rothera test, 4 subjects showed ketonuria at Churchill. These same subjects showed none at Fort Nelson but 3 other men previously negative did show ketonuria at Fort Nelson. In healthy active young men the causes of true ketonuria include complete starvation, a very high ratio of fat to carbohydrate in the diet, and the normal ketosis resulting from work without food as described by Courtice and Douglas (6). A false positive Rothera reaction has been described in samples of urine collected after the ingestion of certain types of biscuits issued in packaged rations (18). Such biscuits were never issued to 'Musk Ox' troops and the Rothera reactions seen in their urine had all the characteristics of a true ketone body reaction. Therefore, we judge that true ketosis was present in a few individuals at both points of examination, but our data do not permit us to decide the cause.

#### *Interrelations among physical fitness and other measurements and tests*

An attempt was made to see if any relation existed between scores in the physical fitness test on the one hand and, on the other hand, any of the measurements made on the troops. Ten men performed the 'pack test' at Churchill and again at Fort Nelson. The difference in the score of a given individual was plotted against the difference in his body weight, hemoglobin, total protein serum ascorbic acid, serum chloride, urine chloride and the rates of urinary excretion of ascorbic acid, thiamine, riboflavin and N<sup>1</sup>-methylnicotinamide. From the scatter diagrams so obtained it was obvious that no degree of correlation existed between changes in the physical fitness scores and changes in any of the measurements listed above.

#### DISCUSSION

From the standpoint of health, fitness and nutrition, exercise 'Musk Ox' differed in important respects from previous recorded North American Arctic journeys. The force was motorized and very mobile. It was supplied by air at all times with fuel and a wide variety of fresh food and packaged rations (table 6). The men were protected against ill effects from the

environment by vehicles and modern protective clothing and equipment, and the men knew that if serious casualties occurred evacuation by air would be prompt. The effectiveness of the planning was shown by our present findings; as judged by clinical examination, physical fitness tests and biochemical studies the troops returned from the journey healthy, fit and well fed. In past times there have been in Arctic travel several common classic diseases and hazards, such as exposure, frostbite, snow blindness, carbon monoxide

TABLE 6. AVERAGE NUTRIENTS SUPPLIED PER MAN PER DIEM TO 'MUSK OX' FORCE FROM DIFFERENT RATION SOURCES

	U. S. ARMY RATION 10-IN-1						CANADIAN ARMY ARCTIC	
	Menu						Ration scale <sup>1</sup>	Mono-pack <sup>1</sup>
	1	2	3	4	5	Average		
Calories.....	3994	4447	4102	4353	4209	4220	5480	5315
Protein, total, gm.....	140	126	144	115	120	129	176	128
Fat, gm.....	142	196	153	198	174	173	256	244
Carbohydrate, gm.....	528	513	530	515	534	524	615	595
Vitamin A, IU.....	8050	1352	1757	820	3269	3050	12400	2090
Thiamine, mgm.....	2.4	2.6	2.8	2.0	3.0	2.6	2.9	2.8
Riboflavin, mgm.....	3.3	2.4	3.7	2.4	3.4	3.0	4.2	3.4
Niacin, mgm.....	27	33	28	32	24	29	38	21
Ascorbic acid, mgm.....	68	66	80	70	79	73	92	75

<sup>1</sup> Calculated from ration items actually delivered to 'Musk Ox' force.

poisoning, 'cold nephritis' (21), psychosis, exhaustion, starvation, scurvy and edema. Exercise 'Musk Ox' experienced to a serious degree only one of these: carbon monoxide poisoning. Certain changes were detected by our observations on the men between the beginning and the end of the journey. The biochemical changes we attribute to changes in acclimatization; the clinical findings to the physical effects of their environment.

In planning for the adequate feeding of troops the most important lessons of the war have been that regardless of environment or type of work troops should be given at all times access to water and calories in amounts enough to cover their day-to-day expenditure; and that soldiers should receive in wide variety types of food which they are accustomed to eat in daily life. On the whole, Exercise 'Musk Ox' was well fed. A variety of common foods was issued in three types of ration, i.e., Canadian Army Arctic Field Service Ration Scale, Canadian Army Monopack Ration (Arctic); and U. S. Army 10-in-1. A good nutritional state was maintained in all respects on the following average daily intake: calories, 4400; protein, 120 mgm., two thirds of it animal; carbohydrate, 520; fat, 190 grams; vitamin A, 4900 IU; thiamin 2.2 mgm.; riboflavin 2.8 mgm.; niacin 26 mgm.; and ascorbic acid

50 mgm. As is usual in Canadian and other armies enough excess was issued to allow for wastage in preparation, cooking and eating. In the present exercise this was in the neighborhood of 15 to 20 per cent of food issued. Maintenance of waterbalance was a definite problem, which did not become acute in Exercise 'Musk Ox'.

The most recent studies in laboratory cold chambers (19, 20) have demonstrated clearly that tolerance to cold is definitely increased by *a*) frequent feedings and *b*) increase in the percentage of calories supplied by fat. 'Musk Ox' troops did eat snacks when able and did voluntarily take 40 per cent of their calories in fat. On the other hand, they developed no craving for fat, thus agreeing in their tastes with Canadian and American troops the world over (14). It is doubtful whether a ration containing much more than 40 per cent of calories in fat would be acceptable even in the Arctic (17). Indisputably, however, the voluntary caloric intake is increased as the environment becomes colder (14), and Operation 'Musk Ox' is a good example of this generalization.

#### SUMMARY

1. Observations have been made on the general health, fitness and nutritional state of members of the Canadian Army Arctic Operation 'Musk Ox', February-May 1946. This was a motorized, air-supplied 3400-mile journey in the winter through the Canadian barren lands.

2. Observations at the beginning and near the end included: *a*) environmental, medical and dietary histories; *b*) physical examinations; *c*) chemical determinations of important constituents of the blood and urine with the aid of an air-borne mobile laboratory; and *d*) tests of physical fitness for hard muscular work. In addition, estimates of food consumption and wastage were made from records of food supplied and from dietary histories. One medical observer travelled with the force throughout the journey.

3. General health, fitness and good nutritional state were well maintained. There was no statistically significant change in average body weight. Values for hemoglobin, serum chloride, rate of excretion of chloride serum protein, serum albumin, serum globulin, serum nonprotein nitrogen, albumin globulin ratio, urine volume, ascorbic acid in the serum, urinary excretion of ascorbic acid, thiamine, riboflavin and N<sup>1</sup>-methylnicotinamide were all within limits found in healthy well-fed white troops in other environments. Scores in tests of physical fitness showed no statistically significant change, being good at the beginning as well as near the end.

4. On the basis of clinical findings and biochemistry no cases were seen of nutritional deficiency syndromes. Of the common classical diseases and hazards reported from previous Arctic travels, only carbon monoxide poisoning occurred.

5. The calculated average daily intake of nutrients was: 4400 calories, 120 grams protein, two-thirds animal; 520 grams carbohydrate; 190 grams fat; 4900 IU vitamin A; 2.2 mgm. thiamine; 2.8 mgm. riboflavin; 26 mgm. niacin; and 50 mgm. ascorbic acid. This proved adequate for the needs of the operation and was provided in the form of fresh and packaged foods, ample allowance being made for wastage.

6. During the journey there was a statistically significant increase in the incidence of certain minor lesions of the skin, lips and mouth. In our opinion, these changes were not associated with disease or nutritional deficiency, but rather were the result of exposure to such environmental stresses as wind, cold and sun and to inadequate facilities for usual personal hygiene.

7. Small but statistically significant changes in chlorides, protein and ascorbic acid occurred. These are interpreted to be associated with processes of acclimatization.

8. Increases in hourly fasting urine nitrogen, phosphorus and creatinine were found; four subjects developed creatinuria during the journey.

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## *Analysis of Tissue and Arterial Blood Temperatures in the Resting Human Forearm*

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QUANTITATIVE ANALYSIS of the relationship between arterial blood and tissue temperatures has not been previously attempted. Bazett and McGlone's measurements of tissue temperature indicate that the deep thermal gradient in the resting normal human forearm does not extend deeper than 2.5 cm.; deeper measurements are not reported (1). According to recent observations in this laboratory, the temperature gradient in intact human biceps muscle extended beyond this depth to approach the geometrical axis of the limb (2), as would be expected if the analytic theory of heat flow by conduction is applicable to a localized arm segment. With the stimulus of this observation, the temperatures of the normal human forearm tissues and brachial arterial blood have been measured to evaluate the applicability of heat flow theory to the forearm in basic terms of local rate of tissue heat production and volume flow of blood.

### TECHNIQUE

Temperature measurements were made with standard thermoelectric technique. The galvanometer system (Leeds and Northrop) had a full sensitivity of 0.75 microvolt per mm. deflection on a scale at 1.0 meter distance, critical damping resistance of 49.0 ohms, period of 1.2 seconds and internal resistance of 18.2 ohms. In operation, sensitivity was reduced by a 90.0 ohm copper-wire resistor permanently in parallel across the galvanometer; this resistor also served to provide a slightly underdamped return deflection on exclusion of the thermocouple from the circuit. The reference junction was sealed permanently in a double-layered vacuum flask container in a thermostatically controlled ( $\pm 0.1^\circ$ ) water bath. Indications of a Beckmann thermometer sealed along side the reference junction did not vary by more than  $0.005^\circ$  in a 3- to 4-hour period. Temperature at the reference junction was approximately  $34.5^\circ$ ; consequently measurements at

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hood of the original level in 30 to 60 minutes. Consequently at least one hour was allowed to elapse after insertion of the *Y*-model thermocouple and the first readings. Figure 3b gives the point of insertion of the needle, the description of the needle and the description of the technique of passage of the *Y*-thermocouple. Definite symptoms of pain referred in a distinct peripheral nerve distribution during the passage of the needle were not

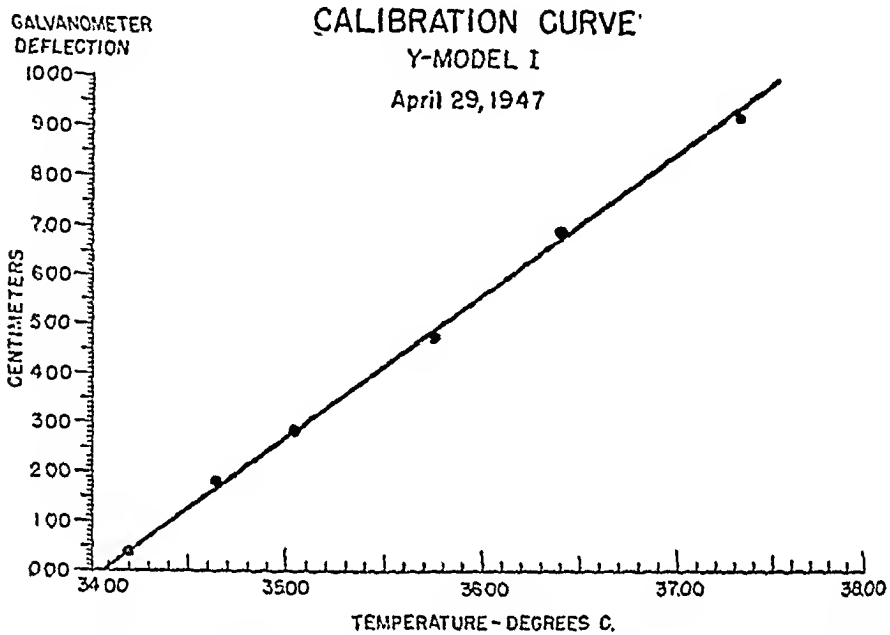


Fig. 2. TYPICAL CALIBRATION CURVE, *Y*-model thermocouple. Temperature coefficient =  $0.34^{\circ}$  per cm.

encountered. When pain was elicited, it was deep and diffuse at the level of insertion; phlegmatic subjects occasionally reported no unusual pain. It is apparent from figure 3c that the path of the needle provides maximum possible distance from arteries and nerves; this was confirmed by dissection of two forearms. The x-rays of figure 5 show the actual relationship of radius and ulna at the experimental transverse plane (I). Both bones are in the lateral half of the forearm (supero-lateral quadrant) because the forearm is pronated.

After insertion of the *Y*-thermocouple into the forearm, the depth of the junction below the skin was regulated and measured by the wire controller of figure 4. This instrument provided constant tension on the two sides of the thermocouple so that no visible slack appeared in the wires. Without fixation of the thermocouple under tension, the wires curled in the forearm tissues and depth estimations were subject to a variable and unknown error (fig. 5a, b and c). The precision of adjustment of position of the junction received an internal check in technique because the total length

of the axis to be traversed by the junction was already known from measurements on the needle of 1b in the forearm (see legend of fig. 3b). Experiments were considered valid only when the total axis measured on passage of junction between lateral and medial skin surfaces coincided within 2.0 mm. with the axis estimated by needle measurements.

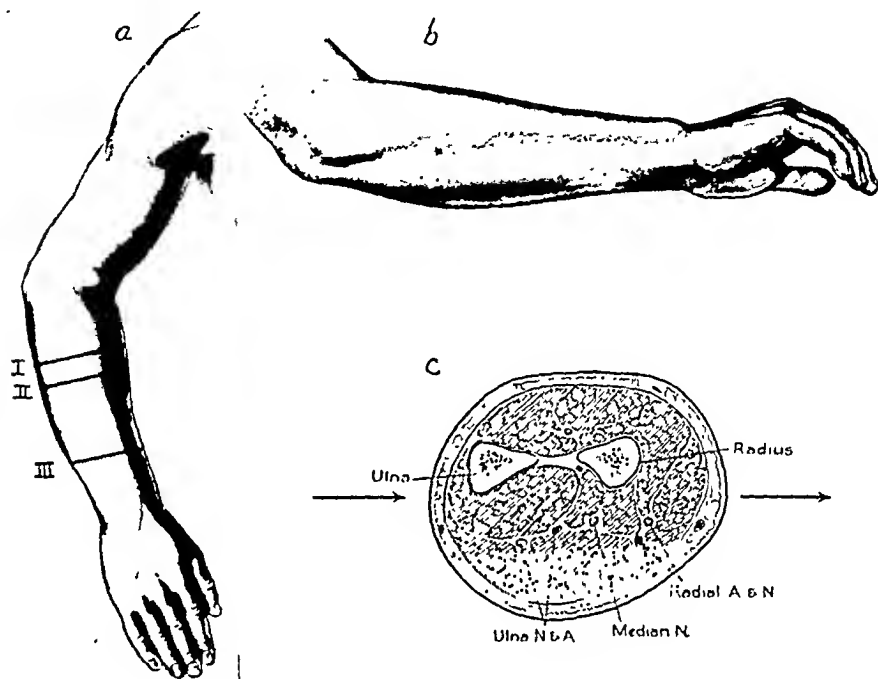


Fig. 3a. EXPERIMENTAL POSITION OF THE RIGHT ARM (superior surface). The pronated forearm was centered between the 2 vertical supports of the wire controller shown in figure 4. The elbow was supported by a soft rubber disc with a central opening just wide enough to receive the medial malleolus of the humerus. The palm of hand was supported on a flat surface of linen towels extended from the head of the metacarpals to the finger tips. Forearm and distal half of upper arm were completely in the air. Inferior aspect of the forearm 5.0 cm. above base of the wire controller (fig. 4). Horizontal line I indicates the plane of passage of the needle; line II indicates the level of figure 3c.; line III indicates the distal plane around the circumference of which temperature was measured in 4 subjects (see section III).

Fig. 3b. EXPERIMENTAL VIEW RIGHT FOREARM (lateral surface). Asterisk indicates point of insertion of the needle of figure 1 (top). This plane was always 8.0 cm. distal to tip of ulna olecranon and midway between superior and inferior surfaces of the forearm. The needle was directed perpendicularly to lateral aspect of the forearm. After penetration of the medial side of the arm, the protruding lengths of needle were measured with millimeter-graduated flexible rule. The sum of these two lengths subtracted from total needle length gave the length of the experimental transverse axis. The thermocouple was drawn into the arm by pulling the needle completely through; the needle was then discarded by clipping lead wire. At end of experiment, the thermocouple was removed by traction on 'active' wire so that the path was reversed.

Fig. 3c. CROSS-SECTIONAL ANATOMY of pronated forearm at level II. Broken arrow indicates path of Y-model thermocouple. (Adapted from Morris's Textbook of Human Anatomy, 9th ed., p. 451, 1933.)

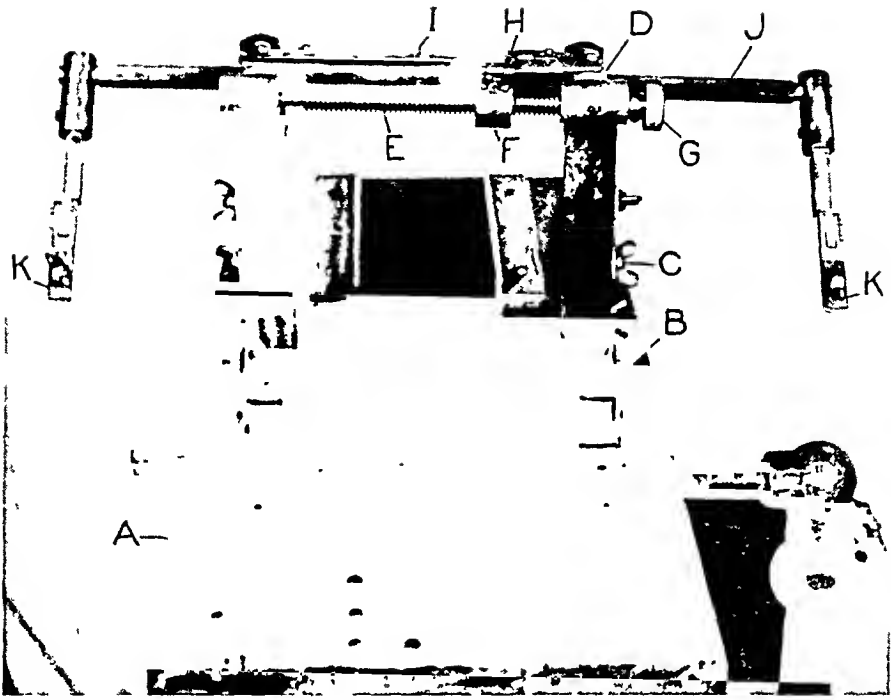


Fig. 4. PHOTOGRAPH OF WIRE-CONTROLLER. The forearm was placed midway between upright supports; elbow at near end of base, hand at far end, experimenter to right. Base, *A*; adjustment along long axis, *B*; adjustment along vertical axis, *C*; universal joint for independent adjustment of right or left side, *D*; worm, *E*; nut, *F*, with slip coupling (not shown); knurled knob for manual control, *G*; position indicator, *H*; millimeter-lined metal scale, *I*; horizontal cross-bar governing movement of wire, *J*; felt-lined clamps for wire, *K*. In operation, the thermocouple wire is stretched taut in the 2 clamps *K* and parallel to the horizontal cross-bar *J*. Manual control of knob *G* causes equal displacements of bar *J* and wire read directly on scale *I*.



FIG. 5

In some subjects, occlusion of the circulation was performed above and below the proximal forearm (plane I, fig. 3a). Occluding pressures of 200-240 mm. Hg were obtained from a reservoir. For interruption of the arterial inflow to the forearm, a 13.0 cm. width blood pressure cuff was used on the midportion of the upper arm. For interruption of the venous return from the distal forearm and hand, a 5.5 cm. width cuff was wrapped about the forearm so that the proximal border of the cuff lay 5.0-7.0 cm. below the level of plane I. Pressures in the reservoir and in the cuffs were read from mercury manometers. In these experiments temperatures were read with the radiometer at the experimental plane I, at the midpoint of the lateral surface *L*, superior surface *S*, medial surface *M* and dorsum of hand *H*. Readings were taken successively at each skin area; interval between readings at the same area averaged 60 to 80 seconds.

## RESULTS

### *I. Comparison of temperature-measurement techniques*

**A. SKIN TEMPERATURE DETERMINATIONS WITH RADIOMETER AND THERMOCOUPLES.** The absolute precision of skin temperature measurement by thermocouples has been questioned by Hardy (4) but supported by Mendelson (5) using a technique of partially imbedding in the skin thermal elements of low mass and heat capacity. Palmes and Park recently reported that temperatures taken simultaneously on the same skin area with a thermocouple assembly and radiometer showed only very small differences (6). The technique described by Mendelson (5) was used to measure skin temperature with thermocouples on the superior surface of the forearm. Four Y-model thermocouples were lined perpendicularly to the long axis of the forearm with the tail and active wire weighted by clamps of 0.58 grams. This amount of weighting was sufficient to cause a faint furrow in the skin, seen on removal. The thermocouples were moved from point to point within a circle of diameter equal to that of the radiometer aperture, measurements being made at each point; between each series of thermocouple readings, a reading was taken from the total area with the radiometer.

Mean thermocouple readings in 6 subjects (table 1) were higher in two subjects ( $0.1^{\circ}$ ,  $0.2^{\circ}$ ), lower in three ( $0.1^{\circ}$ ,  $0.1^{\circ}$ - $0.2^{\circ}$ ,  $0.2^{\circ}$ ) and coincided with the radiometric reading in one subject. Even taking into account the

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Fig. 5. X-RAY PHOTOGRAPHS OF FOREARM to illustrate technique of introduction of Y-model thermocouple. A. Needle of fig. 1 (top) in place after passage through forearm at experimental plane I. B. Lead wire of thermocouple (Y-model) has been drawn into place in forearm. No tension on wire. Note slack in wire, introducing unknown and variable error in depth estimations. C. Lead wire drawn taut in clamps of the wire controller (fig. 4, K). Note that the needle of 5a and the wire in 5c follow identical paths.

fact that relative precision of the radiometric determination was only  $\pm 0.1^{\circ}$ , these findings do not support Hardy's conclusion that an absolute accuracy of  $1.0^{\circ}\text{C}$ . is the best that can be expected by thermocouple technique (4).

Typical spatial variations of temperature are seen in figures 6a and 6b. The maximum differences observed between adjacent points separated only 5-7 mm. are  $0.31^{\circ}$  (fig. 6a) and  $0.23^{\circ}$  (fig. 6b); mean of this maximum difference for the 6 subjects was  $0.38^{\circ}$ . Maximum difference between any two points lying within the radiometer aperture was  $0.67^{\circ}$  for the subject of figure 6a and  $0.47^{\circ}$  for the subject of figure 6b, with a mean of  $0.73^{\circ}$  for

TABLE 1. COMPARISON OF TEMPERATURE, SUPERIOR SURFACE PROXIMAL FOREARM WITH THERMOCOUPLES AND HARDY RADIOMETER

THERMOCOUPLE READING (mean of 16 points) °C.	RADIOMETER READING °C.	ROOM TEMPERATURE °C.
34.24	34.0	25.8
30.93	31.2	26.0
32.75	32.9	26.5
33.48	33.6	26.5
34.98	35.0	26.7
34.63	34.5-34.6	26.6

the 6 individuals. These differences could not be correlated with observable variations in vascular patterns; the superior surface of the forearm usually showed no discernible veins. Mendelson likewise reported that skin temperatures in the arm differed by as much as  $0.5^{\circ}$  at points less than 1.0 cm. apart (5).

B. COMPARISON OF DEEP TISSUE TEMPERATURES WITH NEEDLE AND Y-MODEL THERMOCOUPLES. The high thermal conductivity of the steel needle thermocouples theoretically should cause a flow of heat from tissue to needle and outward flow along the needle shaft. The same factors should also operate with the Y-model thermocouple, but the disturbance of tissue

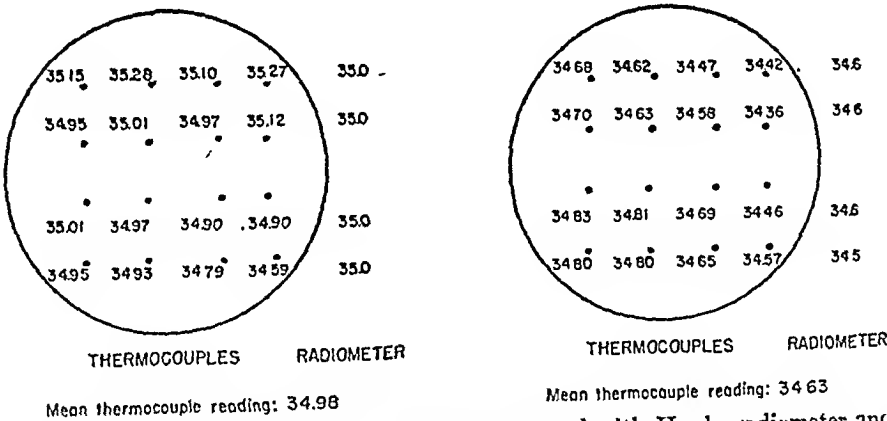


Fig. 6. COMPARISON OF SKIN TEMPERATURES measured with Hardy radiometer and with thermocouples. Measurements made on superior surface, proximal forearm.

temperature should be less because of the much smaller dimensions of these thermocouples. Although theoretical calculations of approximate nature could be made of the heat conducted along needle and *Y*-models for a given temperature gradient, the actual lowering of tissue temperature thereby produced would depend on the character of the tissue temperature gradients and the theoretical analysis would become quite insecure. Moreover, in such a calculation the effect of other factors attendant on thermocouple technique is ignored. Bazett and McGlone devised an empirical correction formula based on various approaches to the problem (1). Their data indicate that the lowering of tissue temperature is least for their smallest dimen-

TABLE 2. COMPARISON OF TISSUE TEMPERATURE READINGS WITH NEEDLE AND *Y*-MODEL THERMOCOUPLES<sup>1</sup>

DEPTH OF INSERTION cm.	NEEDLE THERMOCOUPLE READINGS °C.	<i>Y</i> -MODEL READINGS °C.
3.5	(a) 36.87	36.88
	(b) 36.85	36.91
	(c) 36.91	36.90
4.0	(a) 36.65	36.70
	(b) 36.65	36.69
	(c) 36.67	36.70

<sup>1</sup> Three needle thermocouples (*a*, *b*, and *c*) tested against same *Y*-model thermocouple in 2 subjects.

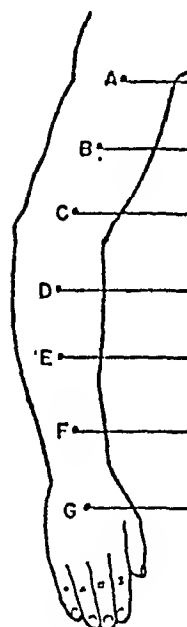
sion needles; the needles used in this study had an external diameter of 0.46 mm. with wall thickness of approximately 0.10 mm. and weight of 0.8 mgm. per mm., being comparable to the needles for which Bazett and McGlone found smallest error. In this study, needle thermocouples were used only (in conjunction with brachial arterial determinations) to find the maximum temperature of the forearm, and for this purpose were always inserted radially to the gradients to a depth of 3.0-4.0 centimeters. If tissue temperature lowering by the needle is significant at this depth of insertion, then the temperature indicated at the same point by the *Y*-model should be higher than for the needle. Direct determinations of temperature at the same point were therefore carried out in two subjects with the two thermocouple types. The *Y*-model was introduced as described and measurements taken until a steady state was obtained. The point of the needle thermocouple was then inserted into the arm 3.0 to 4.0 mm. away from the point of entrance of the wire. By means of a specially constructed angular controller, the needle was advanced till its thermojunction lay a calculated 2.0 mm. from the *Y*-model thermojunction.

In five instances, the needles gave lower indications ( $-0.01^{\circ}$  to  $-0.06^{\circ}$ ); in one instance, the needle gave a higher indication ( $+0.01$ , table 2). These



differences either fall within the limits of precision of the technique or barely exceed those limits. During the insertion of the various needles, the galvanometer deflection caused by the *Y*-model was continuously observed. No change in deflection was noted as the needles reached their final position in tissue; this ruled out the possibility that the needles really did lower tissue temperature significantly, with an effect extending to the junction of the *Y*-model. In order to determine the absence of contact between needle point and *Y*-model thermojunction, the needle was advanced

TABLE 3. TEMPERATURE DISTRIBUTION, LONG AXIS OF ARM, SUPERIOR SURFACE. RADIOMETER READINGS. VALUES IN °C.



	Subject (°C)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)
A	32.3	32.1	33.9	32.4	33.4	33.6	35.4	35.2	34.0	34.2	33.2	34.4	34.4	34.0
B	31.6	31.1	34.0	31.9	33.3	33.7	35.7	33.3	33.8	34.0	33.1	34.4	34.4	34.1
C	31.4	32.3	33.8	31.5	33.3	33.8	35.0	33.3	33.4	33.4	32.4	34.5	34.0	34.3
D	31.5	32.3	33.8	31.5	33.2	34.5	34.7	33.7	33.5	33.8	31.9	34.9	34.1	34.7
E	31.7	31.8	33.8	31.3	33.1	34.2	34.7	33.2	33.6	33.6	31.7	34.7	33.8	34.8
F	32.4	32.8	32.7	31.0	33.3	34.6	34.7	33.5	33.8	33.9	31.7	34.8	34.1	34.7
G	33.5	34.6	31.7	29.9	33.5	33.0	35.7	33.8	34.5	34.5	31.9	35.0	34.8	35.6
Room Temperature	25.0°	25.0°	25.5°	25.5°	25.5°	25.5°	26.0°	26.0°	26.0°	26.0°	26.0°	26.5°	27.0°	27.5°

forward and backward 2.0 mm., and the readings repeated; the same values were obtained within the limits of precision of measurement. Such small displacements of the needle caused insignificant change in the temperature indication because the measurements were being made on the flattest portion of the temperature-depth curves (fig. 15). Heat loss along the two thermocouples must then have differed insignificantly at depths of 3.5 to 4.0 cm. because the same temperature indications were obtained. The heat loss along the thermocouple is theoretically proportional to the temperature gradient; at these depths the gradient in the neighborhood of the junction is quite small and this must be a major factor in the virtual equality of the indicated temperatures. It is possible, however, that the heat loss was less for the *Y*-model and that more intense inflammation about the needle raised the temperature locally.

## II. Skin temperature distribution along the long axis of the upper extremity

The analysis of the depth-temperature curves found at plane I of the forearm (fig. 15) would be considerably simplified if the temperature gradient along the long axis of the forearm were negligible. Consequently, skin temperature determinations were made on the superior surface of the arm, with radiometric technique at the points indicated in tables 3 and 4 and with typical curves plotted from these data in figures 7 and 8.

TABLE 4. TEMPERATURE DISTRIBUTION, LONG AXIS OF FOREARM, SUPERIOR SURFACE. RADIOMETER READINGS. VALUES IN °C.

	Subject (23)	(24)	(25)	(26)	(27)	(28)	(29)	(30)	(31)	(32)	(33)	(34)	(35)	(36)
A	31.9	31.9	31.0	33.2	31.6	32.3	34.0	33.6	33.8	32.6	34.6	33.5	34.8	34.9
B	31.8	31.7	33.2	33.3	31.6	32.0	33.8	33.7	33.8	32.6	34.3	33.5	34.5	34.4
C	31.8	31.5	33.2	33.4	31.6	31.9	33.8	33.8	34.0	32.6	(34.5)	33.5	34.5	34.4
D	31.8	31.8	33.0	33.1	31.3	32.5	33.9	33.9	34.4	32.6	34.7	33.4	34.5	34.5
E	31.9	(32.3)	32.9	33.2	30.0	33.9	33.8	33.9	34.6	32.3	34.5	33.3	34.0	34.6
F	32.3	32.9	33.4	33.6	29.1	(34.1)	33.9	33.8	34.9	33.8	(34.6)	33.9	34.0	35.3
G	34.4	33.6	35.0	33.8	29.4	34.3	35.0	34.8	35.3	34.3	34.7	34.5	34.3	35.0
Wrist Temperature	25.6°	25.0°	25.5°	25.5°	26.0°	26.0°	26.0°	26.0°	26.0°	26.5°	26.5°	27.0°	27.0°	27.5°

The longitudinal temperature gradient along the proximal one third of the forearm (centered between positions D-E, table 3 and fig. 7; centered about B, table 4 and fig. 8) was flatter than along the more distal portion of the extremity. Mean temperature difference (independently of algebraic sign) between successive positions of the forearm was as follows (calculated from table 4): A-B, 0.2°; B-C, 0.1°; C-D, 0.2°; D-E, 0.4°; E-F, 0.4°; F-G, 0.8°. Since distance between adjacent points averaged 5.0 cm., the mean gradient between A and B was 0.04° per cm. and between B and C was 0.02° per centimeter. These gradients were negligible in comparison with the radial gradients at plane I. The break in the mean temperature curve occurred near the junction of proximal and distal portions of the forearm, with a steeper slope between wrist and hand. The uniformity of temperature along the longitudinal axis in the proximal one third of the forearm is, in all probability, partly a function of the more uniform contour of this arm segment in contrast to the distal narrowing and flattening of the limb.

Three types of temperature distribution along the long axis were found for the entire arm (fig. 7): a higher temperature in distal forearm or hand than in proximal arm occurred in 8 subjects; a lower temperature in 4 subjects; and negligible ( $\pm 0.1^\circ$ ) differences in 2 subjects. Likewise for the forearm (fig. 8): a higher distal temperature in 11, a lower in 2, and uniform temperature in 1 subject.

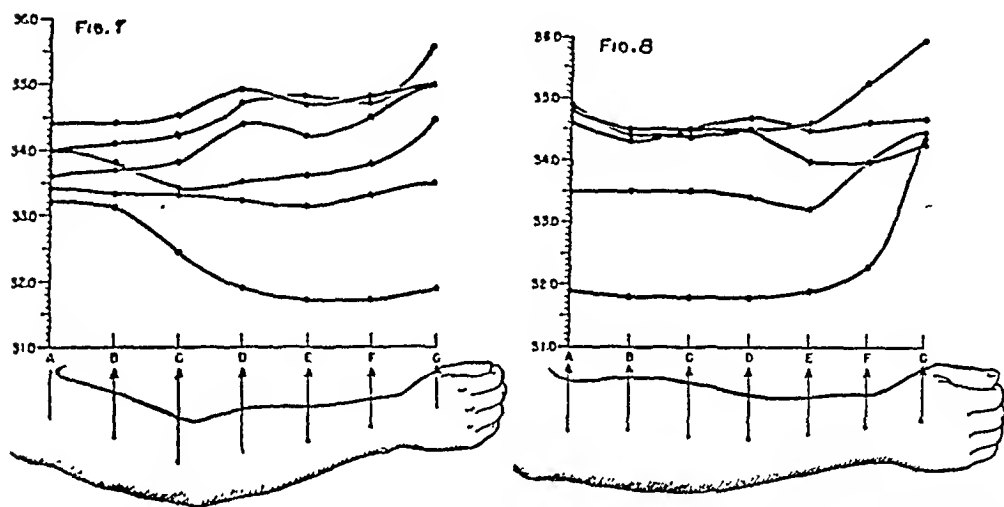


Fig. 7. TEMPERATURE DISTRIBUTION, long axis, superior surface of arm. Measurements with radiometer. Note 3 major types of distributions, described in text. Note the relative absence of gradient in the proximal half of forearm.

Fig. 8. TEMPERATURE DISTRIBUTION, long axis, superior surface of forearm. Measurements with radiometer. Note 3 major types of distribution, described in text. Note the relative absence of gradient in the proximal half of forearm.

Statements occur in the literature to the effect that the hand surface is relatively cool or that there is a tendency for skin temperature to be higher near the trunk (5, 6). The above data indicate, however, that the distal forearm and hand tend to be warmer than the proximal arm at room temperatures of  $25.0$  to  $27.5^\circ$ . This fact is supported by figures given by Stewart and Haskell, the measurements being taken at a room temperature of  $27.0^\circ$  and humidity of 50 per cent (8). The dynamics involved are partly revealed in the data of Roth *et al.* to the effect that maximal finger skin temperatures of  $33$  to  $35.0^\circ$  are reached at room temperatures of  $25.0$ – $26.0^\circ$  (9).

The thermal distribution along all four surfaces of the forearm was studied to see if the gradient present on the superior aspect were present on the other three surfaces. In figure 9 the superior surface shows the typical distal rise of temperature in all three subjects. The same effect is seen in the medial and lateral surfaces in one subject and in all other three surfaces in the other two subjects.

### III. Skin temperature distribution around the circumference of the forearm

Further simplification of the analysis of the deep tissue temperature curves would be possible if the cutaneous circumference of the forearm at plane I were at uniform temperature. Radiometric measurements were therefore made of temperature at successive points 1.0 to 2.0 cm. apart around the entire circumference of the forearm at plane I and in a few instances at plane III.

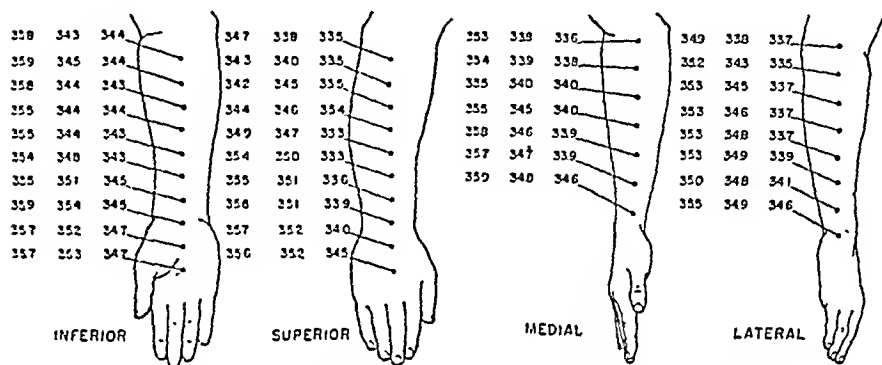


Fig. 9. TEMPERATURE DISTRIBUTION along all 4 surfaces of forearm. Measurements with radiometer. All values are given in °C.

Isothermal conditions were never found around the circumference of planes I or III (table 5, fig. 10). The distribution of temperature followed an irregular and unpredictable pattern from subject to subject. Maximum difference around the forearm circumference ranged from 0.7 to 2.6°. Average maximum difference for the group of 17 subjects was 1.2°. Highest temperature occurred over the medial half in 12 subjects, lateral half in 3 subjects and over both halves in 2 subjects. The most common distribution was a minimum in the supero-lateral quadrant and a maximum in the supero-medial or infero-medial quadrants (7 subjects; see *subject 35*, fig. 10).

Readings from the supero-lateral quadrant were taken from skin over the subcutaneous surface of the ulna. Possibly the predominant occurrence of minimum temperatures in this quadrant is due to the presence of superficial bone and to the fact that the medial half of the forearm contained all soft tissue. For this reason, the circumferential distribution of temperature was explored at both levels I and III in 4 subjects, because at level III the radius occupies the medial compartment of the arm, and bone and soft tissue are more symmetrically placed than at level I. Practically the same distributions were found at both levels in 3 out of 4 subjects (table 5, fig. 10), thereby excluding asymmetry of bone and soft tissue as a sufficient



factor. During the measurements the medial surface of the forearm faced the trunk of the subject, the distance between the two surfaces being about 30 cm. Because of the relatively high skin temperature of the trunk, heat loss by radiation from the medial side of the forearm might well have been lower than from the lateral side which radiated out to the walls of the laboratory and intermittently to the body of the investigator. This factor could not be sufficient in itself to account for the characteristic higher temperature on the medial side, because of the cases in which this temperature distribution was not found, but it is probably contributory. All forearms had a more or less prominent basilic vein on the lateral aspect which coursed inferior to the posterior border of the ulna before dipping downward and around to the infero-medial aspect of the arm; the superior surface of the forearm usually contained no large veins; the medial and inferior aspects of the forearm always bore a variable number of conspicuous venous channels.

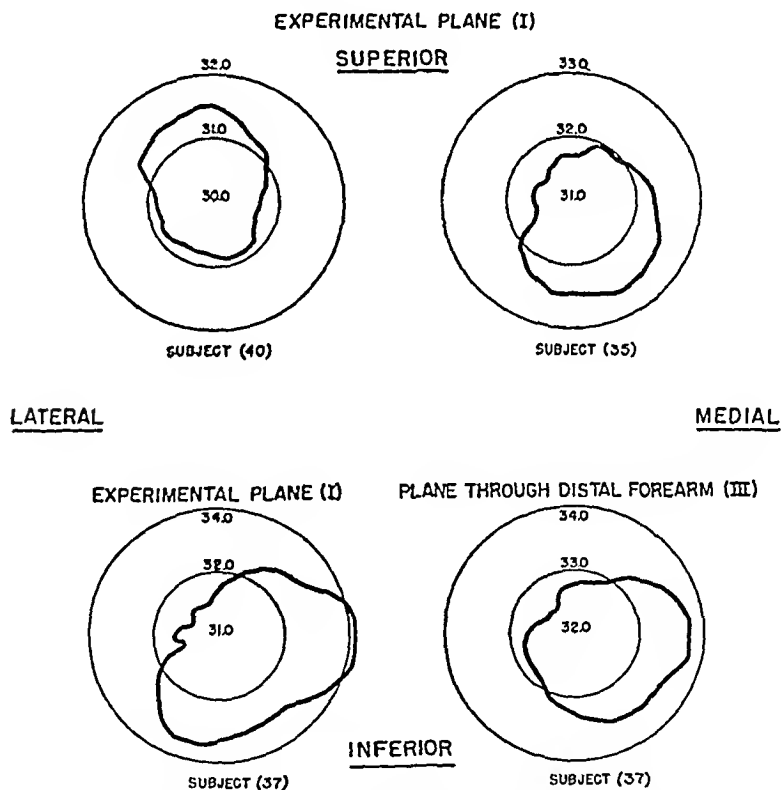


Fig. 10. TEMPERATURE DISTRIBUTION around circumference of forearm at planes I and III. *Subject 35* illustrates the most common type of distribution: minimum in supero-lateral quadrant and maximum in infero-medial (or supero-medial) quadrant. *Subject 40* shows the second most common type of distribution. *Subject 37* shows that the form of the distributions at planes I and III is similar.

The most frequent occurrence of maximum temperatures on the medial side of the forearm may be causally related in part to the greater venous density in this area as compared with the relative paucity of veins in the superolateral quadrant.

Foged found with mercury thermometers in a large series of normal subjects at a room temperature of  $24.0-25.0^{\circ}$  that the maximum mean difference between two positions on different surfaces of the forearm was  $1.1^{\circ}$

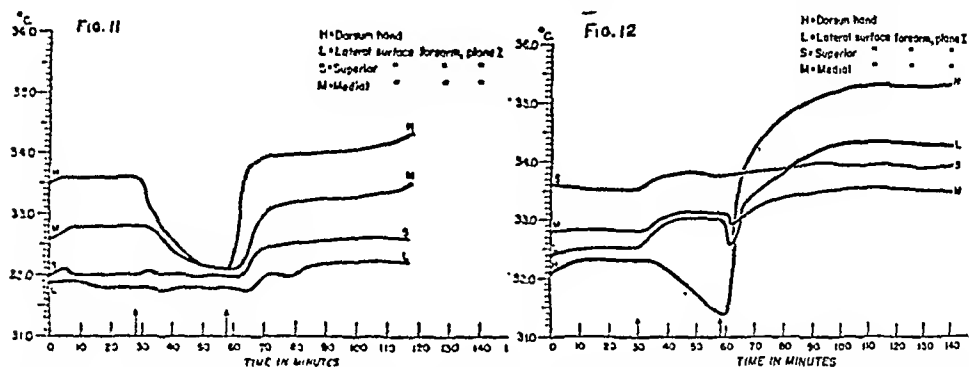


Fig. 11. COMMON TYPE OF RESPONSE to circulatory occlusion, distal forearm, on skin temperature of proximal forearm and hand.

Fig. 12. UNUSUAL TYPE OF RESPONSE to circulatory occlusion, distal forearm, on skin temperature of proximal forearm and hand.

(anterior and lateral). This compares with the value of  $1.2^{\circ}$  given above; however his measurements were taken with the forearm apparently in supination and in contact with the bed along its entire length (10).

#### IV. Effect of circulatory occlusion at distal forearm and upper arm on proximal forearm and hand temperatures

If the temperature differences around the circumference of the proximal pronated forearm are caused only by local variations in cutaneous flow patterns, then interruption of the arterial inflow should disturb this non-isothermal state. Occlusion of the distal venous return should also have an effect if this circulatory variable is contributory.

##### A. EFFECT OF CIRCULATORY OCCLUSION AT DISTAL FOREARM: VENOUS RETURN FROM DISTAL FOREARM AND HAND INTERRUPTED; FLOW THROUGH EXPERIMENTAL SEGMENT INTACT

This procedure, performed in 11 subjects, produced the following effects on forearm temperatures. a) Five subjects had no significant change ( $\pm 0.1^{\circ}$  or less) at any of the three skin areas, L, S and M, during occlusion periods lasting 24 to 40 minutes. Of these, 2 showed no effect on readmission of the circulation to the distal forearm and hand; 1 had a rise in temperature at all three areas; 2 had temperature rises at one or more areas, L, and L and M. b) Five subjects had temperature decreases at one or more skin areas during

the circulatory arrest. Of these, 2 showed drops at *L*, *S* and *M* of  $0.9^{\circ}$ ,  $0.5^{\circ}$  and  $2.0^{\circ}$  and  $0.7^{\circ}$ ,  $0.4^{\circ}$  and  $0.7^{\circ}$ , respectively, for occlusion periods lasting 38 and 36 minutes; on readmission of the circulation temperatures rose quickly to, but not above, their original levels. Two subjects showed decreases at *M* only of  $1.3^{\circ}$  and  $0.7^{\circ}$  for occlusion periods lasting 32 and 30 minutes; on release of occlusion, temperature rose above its original level at *M* in the first, and at *L*, *S*, and *M* in the second (fig. 11). One subject responded with a decrease at *L* and *M* of  $0.7^{\circ}$  and  $0.3^{\circ}$  for a 40-minute occlusion, with significant rises above control levels at both these areas on release of occlusion. *c*) One subject showed a rise in temperature at *L*, *S*, and *M* of  $0.5^{\circ}$ ,  $0.3^{\circ}$  and  $0.3^{\circ}$  during 28 minutes of circulatory arrest (fig. 12).

During the period of occlusion, temperature of the hand fell progressively. The higher the temperature of the hand, the steeper the initial rate of cooling. When initial hand temperatures were between  $34.0$  to  $35.0^{\circ}$ , the total drop ranged between  $2.0$  and  $2.6^{\circ}$  for occlusion periods ranging from 28 to 40 minutes. With initial hand temperatures between  $32.0$  to  $34.0^{\circ}$ , the drops ranged from  $0.6$  to  $0.9^{\circ}$ ; with an initial hand temperature of  $30.6^{\circ}$ , the total drop was only  $0.2^{\circ}$  for a 23-minute period of occlusion.

In the 5 subjects who had a decline in temperature at one or more forearm points during distal occlusion, the dorsum of the hand was  $0.2^{\circ}$ ,  $0.5^{\circ}$ ,  $0.7^{\circ}$ ,  $0.7^{\circ}$  and  $1.0^{\circ}$  warmer than the warmest area at plane I. Figure 9 indicates that a relatively warm dorsum of the hand is accompanied by a higher temperature of entire distal forearm as compared with proximal forearm. This suggests that the temperature declines in these 5 subjects were initiated by removal of a warming influence of the venous return from the distal extremity. However, of the 5 subjects without significant response during circulatory arrest, 3 had hand temperatures  $0.6^{\circ}$ ,  $0.7^{\circ}$  and  $1.4^{\circ}$  higher than that of the warmest area of plane I, and 2 had hand temperatures  $0.5^{\circ}$  and  $0.6^{\circ}$  cooler than the coolest area. The one subject showing a rise in temperature during occlusion had a hand temperature  $0.4^{\circ}$  lower than the coolest area of plane I. Lack of uniformity in response may well be caused by the important probability that change in volume flow to proximal forearm above the occluding cuff was a complicating factor.

After the release of distal occlusion 8 of the 11 subjects showed considerable rises in forearm temperature above control levels at one or more areas; no subjects showed drops in temperature in the period after release of occlusion. Hand temperatures in all subjects rose very sharply on readmission of the circulation to exceed the original level; in general, the lower the initial hand temperature before occlusion the greater the increment of temperature over this level on restoration of the circulation. The rises in proximal forearm-skin temperature were undoubtedly caused by flooding of this skin by



the increased volume return of venous blood from the distal forearm and hand during their reactive hyperemia period. During the early part of this period, reddening of the skin about the basilic vein was quite marked together with a slight swelling of this vessel. Changes over position *S*, during or after occlusion, either did not occur or (with the exception of one instance) were less marked than at *L* or *M* (fig. 12); this correlates with the relative scarcity of large veins on the superior aspect of the forearm.

Just prior to the release of occlusion of the distal circulation, the temperature at plane I was remeasured around the entire circumference in each subject. In subjects not responding during the occlusion period, the non-isothermal condition that was initially present was naturally not affected. In responding subjects, the contours of the temperature distribution were altered with usually small ( $0.2-0.3^{\circ}$ ) reductions in the maximum thermal difference at plane I, but uniform temperature was not achieved (fig. 13, *left*). During occlusion, the circulation to forearm above the cuff was maintained since the proximal margin of the cuff was 5.0 to 7.0 cm. distal to plane I; therefore, flow in the superficial veins at this plane must have continued.

The effect of distal flow in subcutaneous veins on skin temperature has been recognized. Lewis and Love found large differences in temperature of skin over and immediately adjacent to the radial vein with the hand immersed in ice water (11). Grant and Pearson found that the warming of forearm skin in response to warming the body could be prevented if the circulation to the hand of that side were arrested (12).

#### B. EFFECT OF CIRCULATORY OCCLUSION AT UPPER ARM: FLOW THROUGH ENTIRE FOREARM BELOW ELBOW INTERRUPTED

Results were virtually identical in 3 subjects. The first effect of arrest of the arterial inflow was a cooling at all three areas of plane I and hand, the initial rates of cooling being steepest at areas of highest temperature. After prolonged ischemia (35-40 minutes), measurement around the entire circumference at plane I revealed an isothermal state to within  $\pm 0.1^{\circ}$  (fig. 13, *right*). Irregular temperature distribution around the circumference of the forearm with circulation intact must be caused by circulatory inequalities on the arterial or venous side. The difference in responses between the area over the basilic vein *L* and medial forearm *M* as compared with the superior aspect *S* of the forearm, as described in section IV A, suggests quite strongly that the pattern of local subcutaneous venous flow is the contributory factor. Of significance is the fact that the asymmetrical relationship of bone and soft tissue in proximal forearm did not prevent attainment of an

isothermal distribution at plane I in the closing minutes of interruption of the arterial inflow.

At the conclusion of such periods (35-40 minutes) of interruption of the arterial inflow, the subjects experienced much pain in the arm, marked weakness of fingers and wrist with marked hypesthesia of the extremity up to the lower cuff border; these changes could be evaluated only fleetingly but grossly corresponded to those described by Lewis, Pickering and Rothchild (13).

#### V. Comparison of rectal, brachial arterial and deep forearm temperatures

In the analysis of the effect of blood flow on the temperature-depth curves of figure 15a, b and c, knowledge is required of the temperature of the blood in the brachial artery at the elbow and of maximum forearm temperature. In contrast to the pronated forearm position used in all other subjects, the forearm was in complete supination to facilitate arterial puncture; the elbow and dorsum of the hand rested on small linen pads and the rest of the forearm was in air. To determine maximum tissue temperature, three needle thermocouples were inserted vertically into the superior aspect of the forearm; one needle was at the midpoint of the transverse axis and the

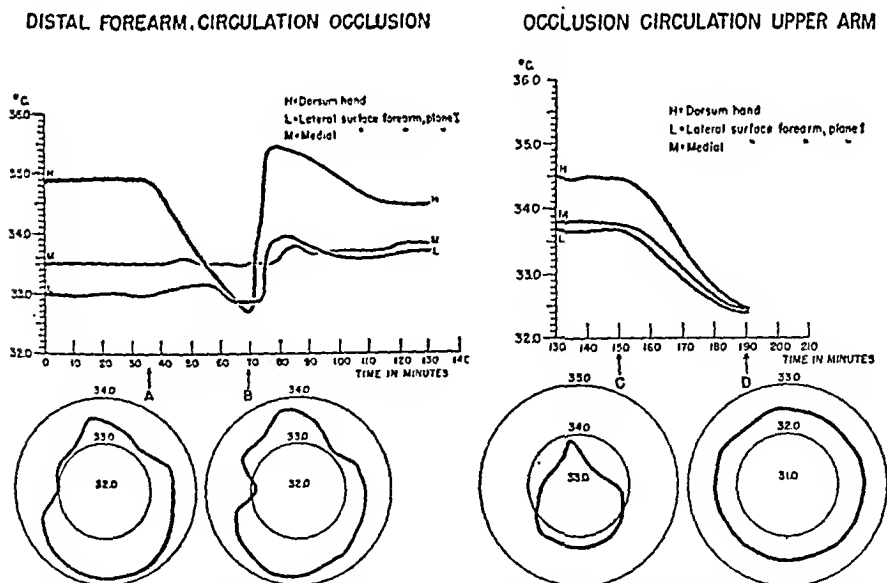


Fig. 13. COMPARISON OF EFFECTS of occlusion of circulation at distal forearm and at upper arm, in same subject, on skin temperature of the proximal forearm and hand. Note only minor changes in surface temperature distribution between A and B at conclusion of period of occlusion at distal forearm. Virtual isothermal state at D at conclusion of period of occlusion upper arm.

others 0.5 cm. on each side. Needles were advanced either until bone was reached or the temperature curve passed its maximum. The two outer needles were then withdrawn and reinserted 1.0 cm. on each side of the mid-point and the process repeated with these. A final withdrawal and insertion were then made 2.0 cm. to each side of the midline.

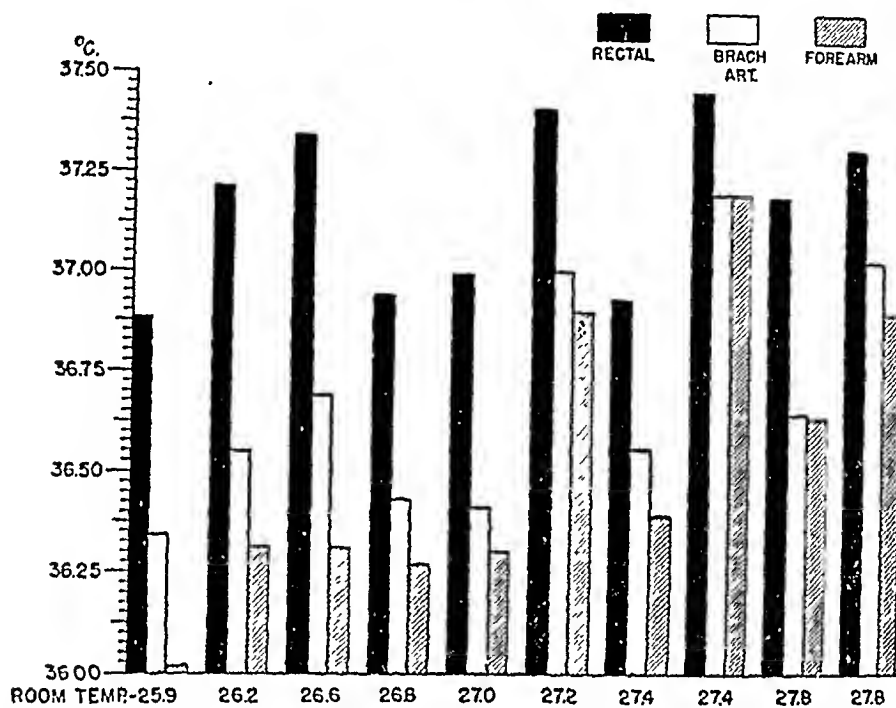


Fig. 14. COMPARISON OF RECTAL, brachial arterial blood, and deep forearm temperatures in 10 subjects.

Brachial arterial blood either equaled or exceeded the deep forearm in temperature in all subjects (fig. 14). The differences ranged from 0.00 to 0.36° with a mean of 0.16°. Mean arterial blood temperature was 36.68°. mean maximum forearm temperature was 36.52°. The arterial inflow to the forearm must act as a warming system for the tissues extending from the skin into the geometrical axis of the limb at plane I if the arterial blood has the same temperature at the elbow and 8.0 cm. below the elbow (plane I). At the range of environmental temperatures covered in these experiments, the difference in temperature between blood in the brachial and radial arteries found by Bazett *et al.* should be minimal; therefore change in temperature of arterial blood between elbow and plane I should be negligible (14). This fact is of importance because the analysis of the contribution of circulation to the observed deep tissue temperature curves of figure 15 is considerably simplified if a unidirectional transfer of heat occurs between blood and tissue throughout the entire tissue.

Foged reported two brachial artery temperature determinations in

man of  $39.1^{\circ}$  and  $37.3^{\circ}$  compared with rectal temperatures in the same subjects of  $37.3^{\circ}$  and  $37.6^{\circ}$ , respectively, at room temperatures of  $22.0$  to  $22.3^{\circ}$  (15). Wright and Johnson found radial artery temperatures  $1.2$  to  $3.1^{\circ}$  lower than oral temperatures in 4 subjects at  $20.5$  to  $24.5^{\circ}$  room temperature (16).

#### VI. Depth-temperature distribution along the transverse axis of the proximal forearm

The form of the thermal gradients through the entire transverse axis of the forearm was determined with Y-model thermocouples by the technique described and illustrated in figures 1a, 3, 4 and 5. At least one hour was allowed to elapse between the insertion of the thermocouple and the

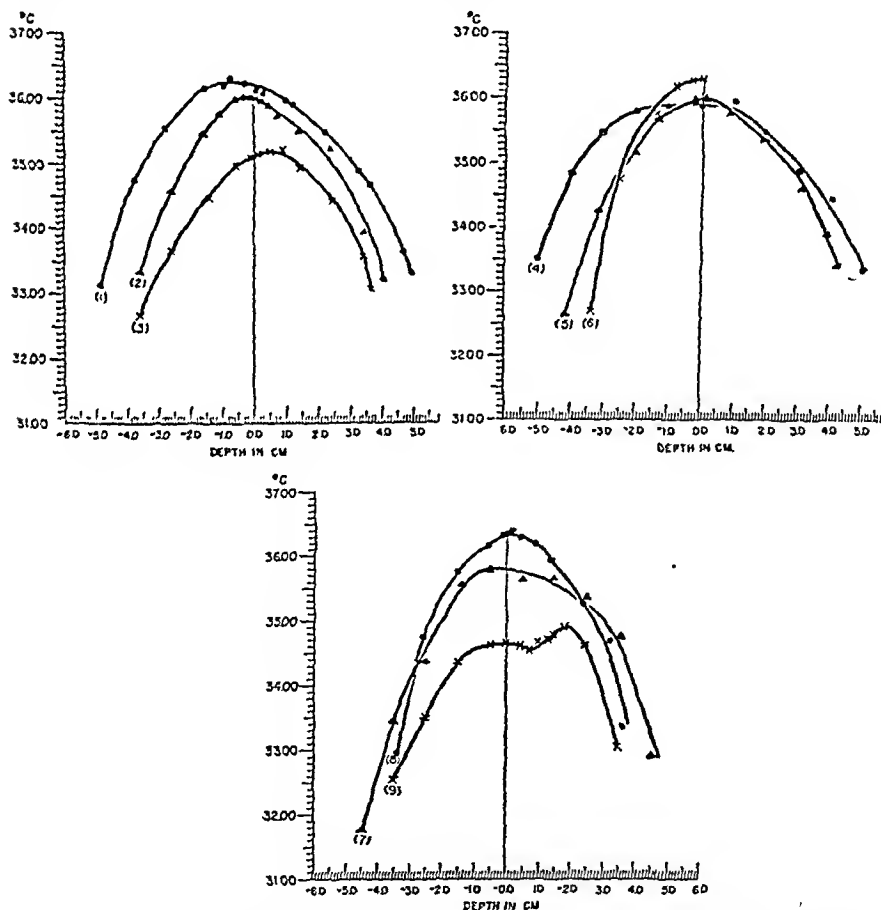


Fig. 15. TISSUE TEMPERATURE-DEPTH CURVES IN 9 subjects; plane I, transverse axis of forearm. See text section VI. Room temperatures: curve 1,  $26.5^{\circ}$ ; 2,  $26.6^{\circ}$ ; 3,  $26.1^{\circ}$ ; 4,  $26.7^{\circ}$ ; 5,  $26.3^{\circ}$ ; 6,  $27.4^{\circ}$ ; 7,  $26.3^{\circ}$ ; 8,  $26.7^{\circ}$ ; 9,  $27.1^{\circ}$ . The negative abscissa values represent the lateral side of the forearm, and the positive values the medial side.

beginning of readings. Skin temperatures could not be determined accurately with these models because the long axis of the junction, 0.1 to 0.2 mm. in length, was oriented perpendicularly to the skin surface and therefore must have been influenced by air and skin temperatures simultaneously before finally entering the tissue completely. For this reason the skin temperatures in figure 15a, b and c were determined with the radiometer placed over the point of entrance and exit of the wire after the thermocouple was momentarily released from the clamps. Readings in tissue at a given point were taken for two minutes. If the temperature remained steady to  $\pm 0.05^\circ$ , the junction was moved to a new position; if not, readings were repeated until a stable figure was obtained. If the readings did not become steady the junction was brought back to the skin surface for a new start. After one complete passage through the forearm, the path of the junction was reversed and readings taken at the same points as on the original passage. The curves of figure 15 are in subjects in whom the temperatures at the same point in the two trips by the junction coincided to  $\pm 0.1^\circ$ . Correspondence of temperatures at the same point on the two passages was always excellent near the axis of the limb and the deviations between the two curves were most marked near the periphery. The curves of figure 15 are for junction passage from the lateral to the medial side of the forearm.

The significant features of the curves of figure 15a, b and c are: 1) In all cases the temperature reached its maximum near the geometrical axis of the limb. This is in accord with the previous findings with needle thermocouples in the human biceps (2). 2) The curves did not possess perfect circular symmetry. Maximum temperature was asymmetrical with respect to the axis by distances varying from 2.0 to 10.0 millimeters without predilection for either side of the arm. In 6 of the 9 subjects, the skin temperature on the medial side was higher than on the lateral side; this corresponds with the detailed results of section III. Since the circumference of the limb was in all probability not at uniform temperature (see section III), each curve must give only the temperature distribution along the experimental axis; the isothermal surfaces inside the forearm cannot be concentric cylinders (approximately) but must possess irregular contours dependent on surface contours. 3) The curves tended to superimpose toward the axis of the limb (except curve 9). Forearm tissue temperature was therefore more uniform centrally than peripherally. Mean maximum forearm temperature was  $36.09^\circ$ . 4) A biphasic curve was found once (curve 9) showing one maximum 4.0 mm. lateral to the axis and a second maximum 1.9 cm. medial to the axis. This distribution of temperature was undoubtedly caused by some local variation in vascular pattern. The path of the needle in all cases was selected to provide maximum distance from ulnar and radial arteries but

the location of the medial peak in curve 9 would seem to correspond to the position of the radial artery, at least with respect to horizontal distance from the axis (fig. 3c).

Logarithmic plots on the lateral and medial limbs of all the curves (except 9) were made by applying two methods: with the zero at the geometrical axis of the limb and with the zero at the point of maximum temperature. Although satisfactory straight lines could be obtained for most of the data points in a majority of subjects, the slopes of the lines in most instances varied considerably with the two methods of plotting, even though the shift of zero was only several millimeters. Exponents ranged in value from 1.57 to 2.83 with a mean value of 2.01 for all plots by both methods. The mean curve of all the data except curves 3 and 9 is plotted in figure 16 for a forearm of average radius of 4.0 cm. Maximum temperature for this curve was at the axis of the limb but again the medial side is at a higher level than the lateral side in accord with the usual findings. Logarithmic plot of the temperature difference between the axis and more distal points against the distance gave a satisfactory straight line for the lateral side with a slope of 2.16; on the medial side the points could not be fitted satisfactorily with a single line.

*Analysis.* The mean curve resulting from a plot of all the data (fig. 16) will be analyzed by an application of the analytic theory of heat flow in homogeneous, isotropic conductors. The symbols are defined as follows:

$\theta$ = tissue temperature, °C.	$E$ = Newton cooling constant in grams cal. per cm. <sup>2</sup> per sec. per °C.
$\theta_a$ = arterial blood temperature, °C.	$h_m$ = rate of tissue heat production in grams cal. per cm. <sup>3</sup> per sec.
$\theta_v$ = venous blood temperature, °C.	$h_b$ = rate of heat transfer from blood to tissue in grams cal. per cm. <sup>3</sup> per sec.
$r$ = normal to cylindrical isothermal surface (radial distance from axis), cm.	$V$ = Volume flow of blood through tissue in grams per cm. <sup>3</sup> per sec.
$R$ = radius of cylinder, cm.	$s$ = specific heat blood in grams cal. per gram per °C.
$K$ = specific thermal conductivity tissue in grams cal. per cm. <sup>2</sup> per sec. per °C. per cm.	

The following assumptions will be made in the analysis. *a)* Since a cross-section of the pronated proximal forearm is almost perfectly cylindrical, the general differential equation of heat flow will be used in cylindrical coordinates. In reality the cross-section is always elliptical with the two axes differing in length by 0.5 to 1.0 cm. The use of elliptical coordinates would involve a degree of complexity in the solution which is probably not justified by the underlying physiological complications.

*b)* The tissues of the forearm must contain two heat sources: heat produced by tissue metabolism and heat transferred from blood to tissue at each point in the forearm. For simplicity of analysis, the rate of heat production

where  $\theta_0$  = temperature at the axis; or by

$$\text{Eq. 7b} \quad \theta = \left[ \theta_s - \frac{(h_m + h_b)}{4K} R^2 \right] - \frac{(h_m + h_b)}{4K} r^2$$

where  $\theta_s$  = temperature at surface of cylinder. Since  $h_b$  is given by equation 3 as a function of  $\theta$ , the differential equation to be solved is (instead of equation 6):

$$\text{Eq. 8} \quad \frac{d^2 \theta}{dr^2} + \frac{1}{r} \frac{d\theta}{dr} + a\theta = b$$

which is a Bessel's equation of zero order in which

$$a = \frac{V \cdot s(k - 1)}{K} \quad b = V \cdot s \frac{(k - 1)\theta_s - h_m}{K}$$

and both  $a$  and  $b$  are numerically negative constants. The physically pertinent solution of equation 8, after appropriate boundary condition substitution, is:

$$\text{Eq. 9} \quad \theta = \frac{\left( \theta_s - \frac{b}{a} \right) J_0(i \sqrt{a} r) + \frac{b}{a}}{J_0(i \sqrt{a} R)}$$

in which  $J_0$  is Bessel's function of an imaginary variable, of zero order and the first kind,  $i = \sqrt{-1}$ , and the absolute value of  $a$  is used in the expression  $\sqrt{a}$ . In order to plot this function,  $\theta_s$  (surface temperature) must be obtained from the Newton cooling law, which is:

$$\text{Eq. 10} \quad -K \frac{d\theta}{dr} = E(\theta_s - \theta_E)$$

where  $\theta_E$  = the environmental temperature (the air and walls of the laboratory being at the same temperature). Applying equation 10 to equation 9 and solving for  $\theta_s$ :

$$\text{Eq. 11} \quad \theta_s = \frac{\frac{b}{K\sqrt{a}} [-iJ_1(i\sqrt{a}R)] + 1.21EJ_0(i\sqrt{a}R)\theta_E}{K\sqrt{a}[-iJ_1(i\sqrt{a}R)] + 1.21EJ_0(i\sqrt{a}R)}$$

in which  $J_1$  is Bessel's function of an imaginary variable of the first order and first kind.

In figure 16, the lowest curve has been plotted for a forearm in which blood flow is assumed to be absent and in which the only heat source is local tissue heat production ( $h_m$ ). The value of  $h_m$  had been calculated as 0.0009 from the data of Asmussen *et al.* and Holling on the  $O_2$  consumption of

skeletal muscle in resting man, taking the respiratory quotient as 0.82 (21, 22). Equation 7b was used in construction of the plot with  $h_b$  equal to zero;  $\theta_s$  was calculated by the Newton cooling law. By use of equations 9 and 11 in which  $h_m = 0.0001$  the dotted curves of figure 16 were plotted to give as close an approximation as possible to the mean experimental data. The arterial blood temperature, not being measured in these subjects, was

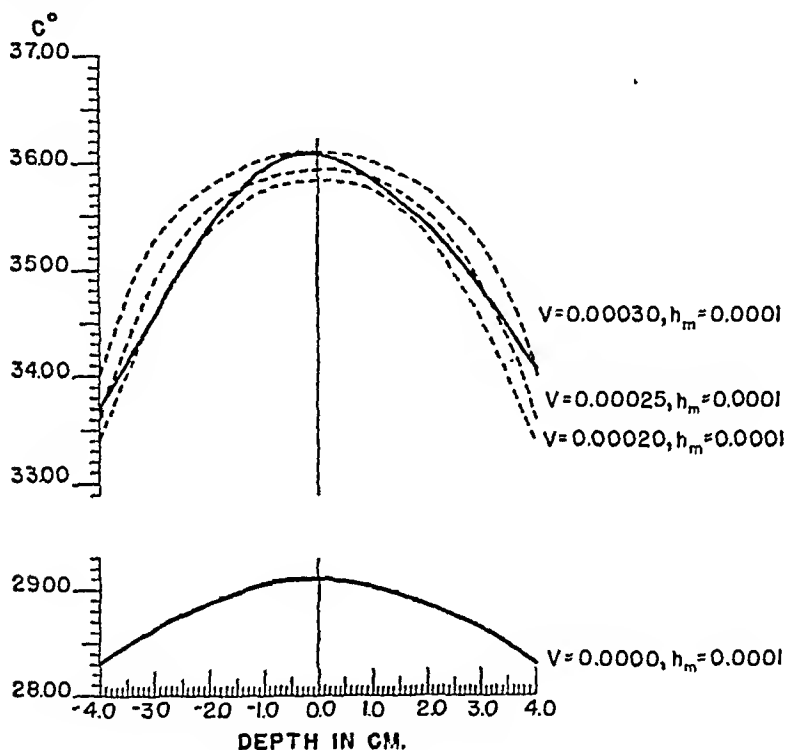


Fig. 16. MEAN EXPERIMENTAL and theoretical curves.

taken at  $36.25^\circ$  or  $0.16^\circ$  higher than the mean maximum tissue temperature in correspondence with the subjects of section V; mean room temperature of  $26.6^\circ$  was used in equation 11; full equilibration ( $k = 0.0$ ) between blood and tissue was assumed. The experimental curve was most closely approximated when the blood flow  $V$  was assigned values from 0.0002 to 0.0003 gram per  $\text{cm}^3$  per second. These necessary values of  $V$  correspond quite closely to the range of 0.00025 to 0.0005 found by Abramson *et al.* (23) and Barcroft and Edholm (24) using plethysmographic technique on the forearm. If partially incomplete equilibration is assumed between blood and tissue ( $k = 0.25$ ), then the values of  $V$  most nearly satisfying the mean curve become 0.0003 to 0.0004; in the unlikely event that equilibration is very



incomplete ( $k = 0.50$ ),  $V$  becomes  $0.0004$ – $0.0005$  gram per  $\text{cm}^3$  per second. The causes of the deviation between the mean experimental curve and the theoretical curves must be numerous. The assumed uniformity of  $h_m$ ,  $V$  and  $k$  must be contributory but experimental check on these assumptions is not possible with existent techniques. It is possible that the venous return from the distal portion of the extremity modified the deep tissue temperature distribution considerably.

#### DISCUSSION

Hardy and Soderstrom (18) and Gagge, Winslow and Herrington (25) have analyzed the relationship between rectal and mean skin temperatures and total heat loss from the body surface in calorimetric experiments on man. In their analyses, the calculated thermal conductance of tissue is considered to be a function of the peripheral blood flow, the physical thermal conductivity of the tissue (and the depth of gradient in the theory of Gagge *et al.*, 25). These authors' conclusion that the peripheral blood flow cannot be a significant factor in heat loss from the skin at the experimental range of room temperatures is not supported by the present analysis. Granted that the values of human skeletal muscle  $\text{O}_2$  consumption given by Asmussen *et al.* (21) and Holling (22) are even approximately correct, then the rate of tissue heat production is much too small to sustain the level of the observed temperature distribution in the forearm. On the basis of the above analysis, a blood flow of  $0.0002$  to  $0.0004$  gram per  $\text{cm}^3$  per second is needed to raise the level of the theoretical distribution to that of the experimental curve; moreover, the values of the blood flow calculated by theory coincide very closely with those obtained by others experimentally (22, 23). With a flow of  $0.0003$  at full thermal equilibration and a rate of tissue heat production of  $0.0001$ , only 25 per cent of the total heat lost from the surface of the proximal forearm would be that produced by local metabolism.

The conclusions drawn from calorimeter experiments are based on mean data for the body surface and the particular thermal relationships found for the forearm do not necessarily apply elsewhere. Gagge *et al.*'s calculation (25) of a mean depth of gradient of 2.2 cm. likewise does not find experimental confirmation in the forearm. An important feature of that calculation, namely the assumption of a peripheral blood flow of zero, obviously is one major source of difficulty. The theoretical blood flow-tissue metabolism curves of figure 16 are almost true parabolas because the infinite power series defining the Bessel's function of zero order and first kind converge so rapidly at the physiological range of values of the constant

$a = \frac{V_s(k-1)}{K}$  that all terms after the  $r^2$  term become negligible. These

theoretical curves deviate most from a perfect parabolic distribution at the periphery of the cylinder, i.e., as  $r$  increases. Burton and Bazett (26) explained the 'paraboloid' character of Bazett and McGlone's data (1) on the basis of equation 5a or 5b, but the above analysis of the blood flow effect leads to a more complete interpretation. The curves of Bazett and McGlone (1) taken in cool environments show a lower level and in addition a steeper initial slope than those taken in warmer environments. This may be accounted for in theory by the fact that reduction in blood flow has the effect of causing an increase in slope at the periphery as well as a reduction in level of the entire curve; in other words, as the blood flow increases the calculated curves become flatter and approach arterial blood temperature but cannot exceed that temperature.

It is apparent that if the blood flow be known, the determination of the tissue temperature distribution and brachial arterial temperature would permit a tentative calculation of the rate of forearm heat production which is subject, however, to the important assumptions already discussed. These assumptions, principally the uniformity of heat production and blood flow, cannot be explored experimentally at present. More extensive analytic study of these assumptions would involve the solutions of differential equations in which both the local rate of tissue heat production and blood flow become functions of the distance from the axis of the limb. Elimination of the necessity for use of the Newton cooling law could be attained by immersion of the forearm in a constant temperature water bath; this would also possess the advantage of rendering the skin surface virtually isothermal with possibly better circular symmetry of the individual curves. In addition, interruption of the distal venous return might also yield individual curves more susceptible to analysis. However, until such simplifying steps are taken, a further complicating theory in the analysis of the curves is not justified.

#### SUMMARY

The cutaneous topography of temperature in the upper extremity has been determined with reference to the presence of gradients and to the effects of blood flow on the proximal forearm.

Simultaneous rectal, brachial arterial blood, and deep forearm temperatures have been measured. Under the condition of these experiments the blood flow acts as a warming agent not only to the superficial tissues but to all the forearm tissue between skin and axis of the limb.

Steady-state tissue temperature-depth distributions have been determined and the analytic theory of heat applied to evaluate the effects of local heat production and circulation.

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## *Patterns of Tremor in Normal and Pathological Conditions<sup>1</sup>*

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UNDER A VARIETY OF CIRCUMSTANCES, normal or pathological, motor activity may take the form of regularly periodic pulses of contraction instead of smooth tetanus. The following account deals with the type of clonic or alternating motion seen typically in paralysis agitans, and also in fatigue or excitement, in senile conditions and in spinal clonus, and under the influence of certain drugs. Although typically alternating in flexors and extensors, variations from a standard pattern occur in various conditions and with various degrees of pathological involvement of motion; and volitional effort affects the pattern characteristically. We have also studied as a reproducible standard of comparison the volitional tremor of which any normal subject is capable and which has the same general pattern as that found in the conditions noted above. The observations were made in terms of electrical activity led from the surface of the skin over the muscles. Whenever feasible the muscles chosen for recording were the triceps as extensor of the elbow, and biceps and brachioradialis as flexors. The latter muscle also works with the forearm muscle group in many movements.

Various degrees of flexion, extension and rotation of the arm were employed to test the effect of volitional effort on tremor pattern. The fundamental physiological factors or components have been sought out of which the various patterns of tremor observed could conceivably be synthesized, or in terms of which they could be analysed. Suitably selected cases were referred to the laboratory from various hospital and clinics, particularly by Dr. Joseph J. Gitt and Dr. Irwin Levy without whose cordial cooperation and clinical consultation this work could not have been carried on.

The relation of the occurrence of this type of tremor to volitional activity, disregarding for the present differences in frequency and other details, may be expressed diagrammatically as in figure 1. In this figure distance along the vertical axis represents for the dash curves intensity of tremor and for the full curves, intensity of overall contraction. The heavy line curve indicates merely that a muscle contracts more with increase in the voluntary effort to contract it, but perhaps not in a linear relation. The light full line curve, to the left of the zero ordinate for the resting or normally relaxed state, represents possible involuntary or unintentional contraction, i.e., rigidity or

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residual tension at 'rest'. Volitional *effort* is then indicated toward the right from this zero, volitional *relaxation* toward the left. The dash curve *A* then indicates the range of activity over which the tremor of 'rest', or Parkinson tremor, is typically in evidence. That is, it appears at rest, can be relaxed or at least reduced consciously and tends to be displaced or covered up by voluntary activity of relatively low intensity. It behaves in fact like an intermittent or rhythmically inhibited form of rigidity, and rigidity is also characteristic of this disease. This relation between rigidity and tremor has been suggested repeatedly.

The dash curve *B* indicates similarly a range of tremor of action, evident in a variety of conditions. This may appear only with voluntary effort, increase with effort up to a maximum, and then be either replaced or masked by more continuous tetanic activity. The curve *C* indicates that with strong effort the normal subject also tends to go into tremor (fig. 2) which again may be converted into an irregular tetanus by maximal exertion. Some cases of action tremor may be looked on as extending the curve *B* over the whole range of effort as indicated at *D*.

This schematic representation is severely simplified, and its justification as a generalization will be more evident below. On the other hand, so many variables enter into the records of individual cases that much of the material to be presented will appear at variance with any classification so categorical as this. The points to be made with relation to this diagram are: first, that tremor is a periodic form of *contraction*, comparable to tetanic contraction except for its periodicity; second, that it typically follows the usual rules of contraction, such as increase and decrease with voluntary effort, reciprocity in opposing muscles, etc.; third, that its abnormalities of pattern correspond in some respects to abnormalities of continuous contraction under comparable conditions; fourth, that increase of effort finally tends to obscure any tremor by filling the intermittent periods of quiescence with tetanic activity; and that in general many of the complications of tremor pattern may be considered as expressions of the underlying pattern of movement in terms of periodic activity.

#### TECHNIQUE

As routine procedure the action currents of three muscles of the arm, biceps, triceps and brachioradialis, were recorded on a Grass inkwriter employing surface electrodes, one on the belly of each muscle and one near the tendon end. A cathode ray oscillograph could be plugged into any channel ahead of the filters. Records were taken at rest, during voluntary or involuntary tremor, with various arm postures, and during various degrees of flexion and extension freely or against resistance, or under combinations of these conditions. Other groups of muscles were recorded as the occasion demanded.

The chief difficulty met with involved extraneous potential variations due to swinging of wires and movement of contacts during violent tremor.

Each set of leads was therefore constructed of three light copper wires one of which was grounded, the other two led to a push-pull amplifier. All were held together except for the terminal 10 centimeters which were covered with a thin coat of cement. This minimized potentials due to movement of a lead wire through a variable potential field. To the terminals of these leads short loops of #24 bare copper wire or metal disks were soldered. The solder joints were carefully insulated and strengthened with cement. The electrodes consisted of drops of a mixture of one-fourth plaster of paris and three-fourths modeling clay applied as a thin paste made up with salt solu-

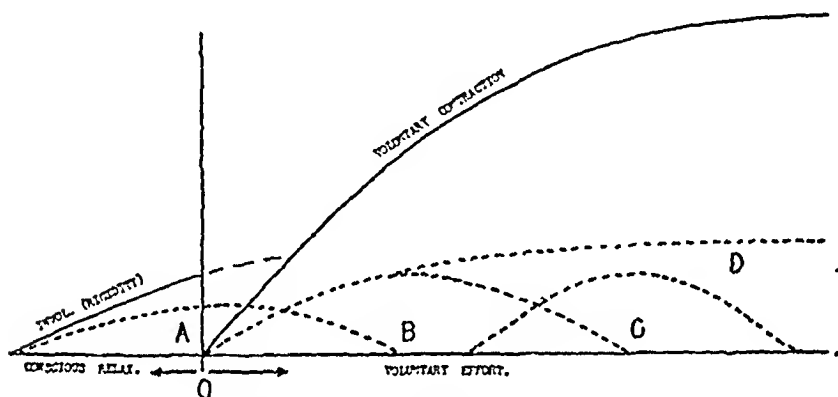


Fig. 1. TREMOR AS THE PERIODIC MODULATION OF ACTION. Scheme relating the occurrence of reciprocal or alternating tremors to degree of voluntary effort. Frequency of the tremor is disregarded in this scheme. A given instance of tremor tends in general to be most pronounced at some limited range of muscular activity, to decrease in intensity with relaxation below this range and to decrease again with greater than the optimal effort. This tendency is represented by the dash-line curves A, B, and C, each of which first rises from the base line to a given maximum and then is suppressed with greater than optimal increase of effort or is obscured by tonic activity. Further discussion in text.

The statement that rigidity can be relaxed voluntarily applies to the residual tonic tension at rest and does not mean that the patient can consciously reduce the resistance to passive movement by which rigidity is detected clinically. This is a point more difficult to evaluate, but seems also to be possible in some cases.

tion. Into each drop of this paste the terminal of a lead wire was inserted before setting. This prevented any movement at a metal-fluid contact. These electrodes adhere to the skin better if a coating of gelatin solution is first applied since the gelatin dries about the edges of the pellet to hold the latter firmly to the skin. This procedure however was usually not necessary. Electrodes without gelatin give satisfactory results for half an hour or more before drying to a high resistance, and are easily replaced. A ground electrode, consisting of a band of thin spring bronze covered with wet gauze and usually wrapped about the upper arm, was connected to a grounded wire.

Usually the first second of volitionally induced tremor will show a rate of one or two beats per second faster than the standard rate, and may then fall off to the standard value only after several seconds. This higher initial rate is apparently occasioned by the greater effort required and by the greater muscle tension induced to start the tremor than the effort necessary to maintain it. The technique of speeding up the rate, once it is established, is to increase muscle tension. The subject may think he is willing a higher frequency; in about half our cases, however, the attempt to increase frequency either fails to show an increase, or results in a decrease.

Increase of frequency then is associated with two changes: an increase in amplitude of each burst and, at least in the extreme, the appearance of activity of the character of tetanus between bursts. That is, the periods of activity encroach upon the periods of quiescence. Finally, the tremor breaks by passage into an irregular tetanus. In some cases this tetanus passes first through a stage of regularly spaced synchronous discharges ('spikes' or twitches) of a frequency between 25 and 30 per second, with no obvious relationship to the previous tremor rate. This appears simply as a tetanus with a higher than usual synchronization of many muscle units. The twitch rate might represent the rate of discharge of each unit. However, there is reason to believe that regularly periodic tremor impulses maintain the synchronization of units in such spike records for in some cases the previous tremor rate persists as a series of spikes above the average in amplitude.

A similar synchronization of motor units which results in spiking in the record occurs in fact in each tremor burst as may be seen in oscillographic records of tremor (fig. 2). Each biceps burst typically consists of one to three or more fairly discrete spikes, each spike to be sure consisting of secondary groups of units out of exact synchrony, but obviously associated closely. That is, each biceps burst may be viewed as a series of several twitch contractions, following at intervals of 10 to 15 milliseconds, or at a rate of 70 to 100 per second. Each burst lasts then up to 50 milliseconds. In contrast to this the triceps burst usually shows a fine structure consisting of twice or more the number of spikes with half the interval between them. The unit burst usually lasts somewhat over 50 milliseconds. The brachioradialis discharge lies between these two muscles with respect to the fine structure of its bursts, resembling more perhaps the biceps with which it cooperates in flexing the elbow. Another difference between biceps and triceps is that the initial spike of the biceps burst is the highest, or may be preceded by a much smaller one, so that the peak of activity comes early in the burst; while each triceps burst is liable to show a symmetrical increase and decrease of amplitude, the highest activity falling in the middle of the

burst. With respect to this differentiation there is considerable variation even within one record. The point of interest here is that as a period of tremor breaks over into tetanus, the biceps muscle units are relatively highly synchronized.

Another form of synchronization can be induced in some normal subjects, but only under such particular conditions that we have not been able to train all subjects to so perform. One necessary condition seems to be an extreme voluntary effort to increase the force of the tremor, but

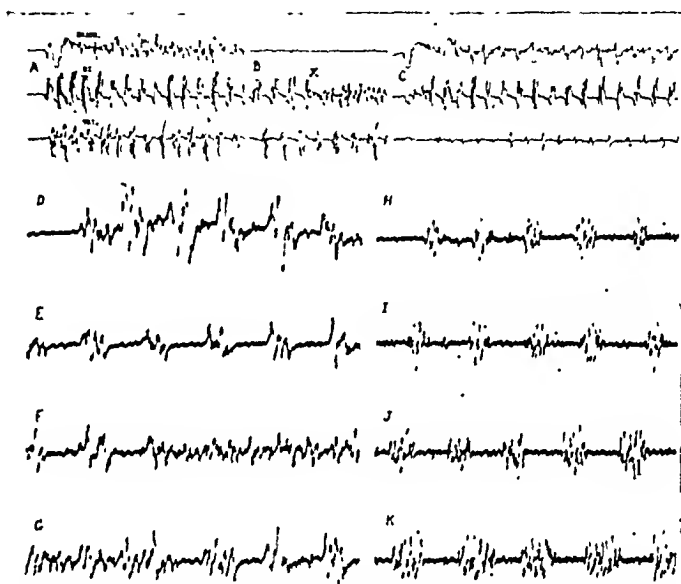


Fig. 2. VOLUNTARY TREMOR OF NORMAL SUBJECT; *A*, abrupt start of tremor, 100-gram weight held in hand, vertical movement of forearm about elbow, 8.5/sec. *B*, shift of movement from vertical to lateral, at *X* biceps shifts from tremor to tetanus, triceps continues tremor. *C*, start of voluntary tremor with 1 kgm held loosely in fingers, 8.5/sec. *D* to *G*, oscillograph records of biceps during tremor recorded in *A* and *B*. *D*, start, 8.5/sec. *E*, maintained at 7/sec. *F*, shift from vertical to lateral movement. *G*, shift back to vertical. *H*, oscillograph record of triceps start in *C*. *I*, slowed to 7/sec. in maintained tremor. *J*, 1 kgm. weight gripped tightly to move with arm, no change in rate with added mass. *K*, triceps during shift from vertical to lateral movement as in *F*, biceps.

without an increase of the frequency to the point of breaking over into a tetanus, and without inducing such activity between bursts as to obscure the discrete discharges. It may thus be viewed as an unusual type of transition in a sequence which more usually shows filling of the tremor intervals to a continuous tetanus, but characterized by a high degree of synchronization of ventral horn cell discharges. This phenomenon has appeared most clearly in the biceps in normal subjects. Its usual course is first the appearance of a group of small spikes between each two bursts



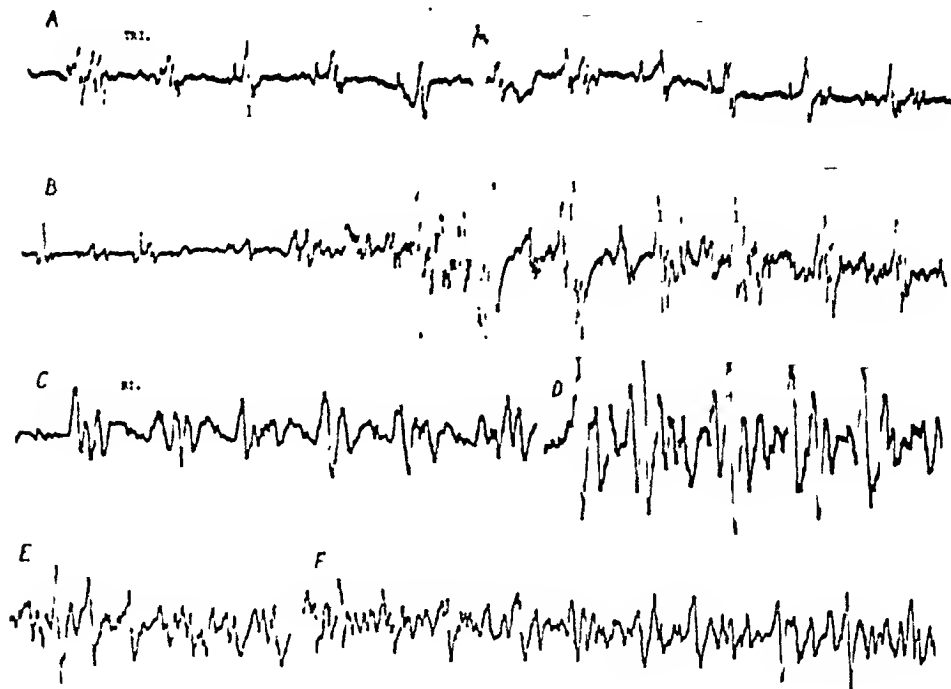


Fig. 3. NORMAL SUBJECT: *A*, after 0.5 cc. adrenalin; resting tremor, triceps, 8.7/sec. *B* start of voluntary tremor, 8.3/sec. *C*, different normal subject, voluntary tremor at 8/sec. in biceps. *D*, stronger effort, increase of rate to 9/sec. *E*, doubling of frequency with maximal effort, 17/sec. with repetitive spikes closing tremor intervals. *F*, same, 2 sec. later in same record, accented spikes at doubled rate with decrementing spike series filling some intervals.

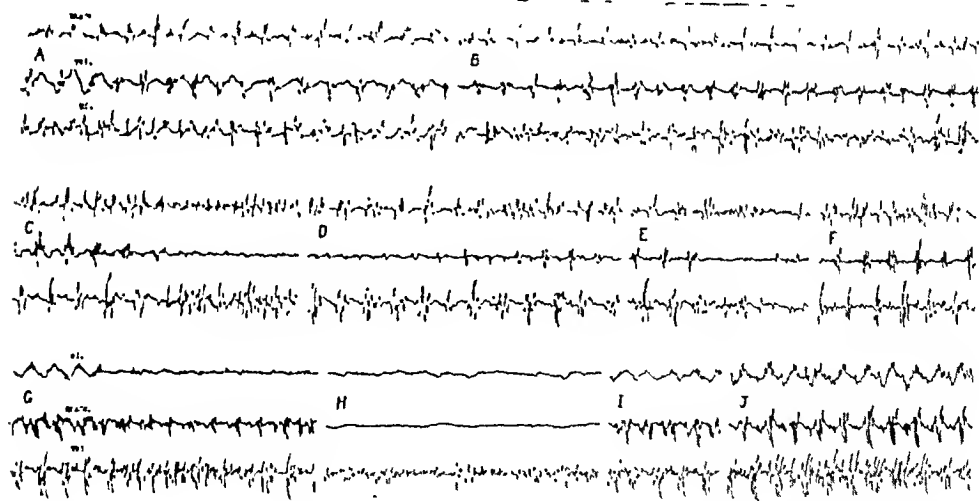


Fig. 4. PARALYSIS AGITANS, illustrating shift of phase from alternate to synchronous in opposing muscles. *A*, rest. Brachioradialis and biceps synchronous, triceps alternate in normal pattern but biceps carries both frequencies. *B*, brachioradialis shows frequency slower than biceps, 4.4 and 4.9/sec., shifting phase continuously throughout this record. One of 2 cases of independent rhythms in different muscles. *C*, start of flexion of elbow. Brachioradialis shifts from biceps to triceps beat just before flexion. Tremor obscured by tetanus in flexors, inhibited in extensor. *D*, return of regular tremor during holding of flexion. *E*, suppression of tremor on relaxation of flexion. *F*, return at rest after flexion, with brachioradialis following tremor rhythms of both biceps and triceps. *G*, another Parkinson subject; extension of elbow suppresses tremor in biceps, tremor persists in brachioradialis. In triceps, tetanus obscures tremor rate, probably doubled. *H*, suppression of tremor by conscious relaxation. *I*, return of tremor after relaxation, doubled beat in brachioradialis, alternate high and low. *J*, extension, traces of doubled frequency.

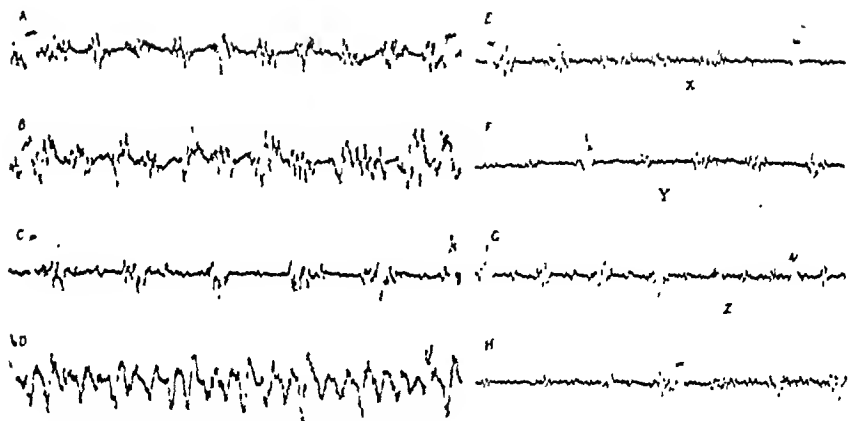


Fig. 5. PARALYSIS AGITANS. Each strip is 1 second of record between square wave signals. *A*, brachioradialis at rest. Doubled rhythm, 10/sec. *B*, same, biceps. *C*, triceps, single rhythm 5/sec., resting. *D*, biceps, weak flexion. Periodic accentuation of spike amplitudes at tremor rate. *E*, triceps, hand in neutral position, rotated to pronation at *X*, with abolition of tremor. *F*, holding in pronation, tremor returns at *F'*. *G*, return to neutral, tremor abolished again at *Z*, and in *H*, after return to neutral, tremor reappears at rest. Supination had a similar effect. Any movement involving flexors inhibited triceps, holding of posture permitted return of triceps tremor.

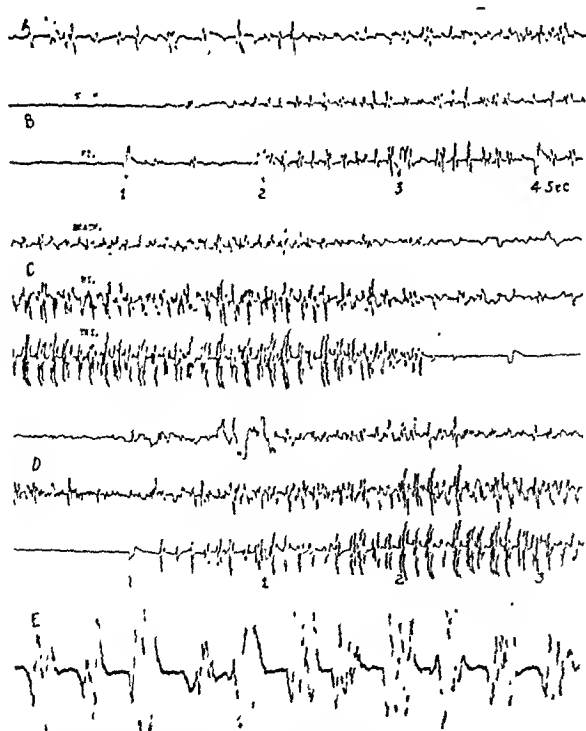


Fig. 6. PARALYSIS AGITANS. Clinically this subject showed chiefly rigidity in left arm, tremor in right. Records from left arm. Absence of overt tremor movement is assignable to synchronous contractions in opposing muscles. *A*, biceps at rest. *B*, start of elbow flexion. Large deflections are time signals at 1 sec. intervals. *C*, during flexion: double frequency, synchronous in all muscles. The resting rate can be followed in biceps record after relaxation, 5.5/sec. During contraction the rate is doubled at 10-11/sec. *D*, weak extension of elbow. *E*, oscillograph

Nearly identical patterns in biceps and triceps, 10.5/sec., doubled frequency. *E*, oscillograph record of triceps between seconds 2 and 3 as marked on lower record of *D*.

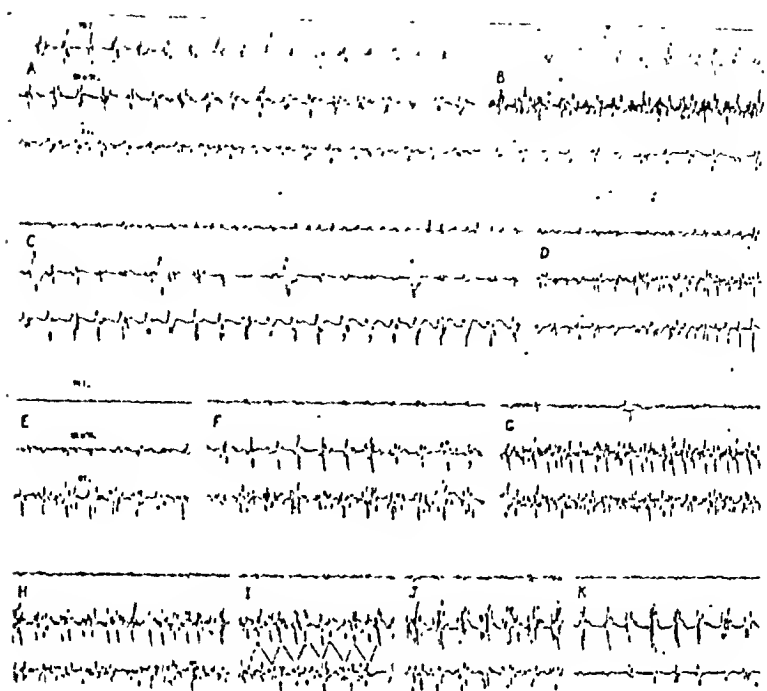
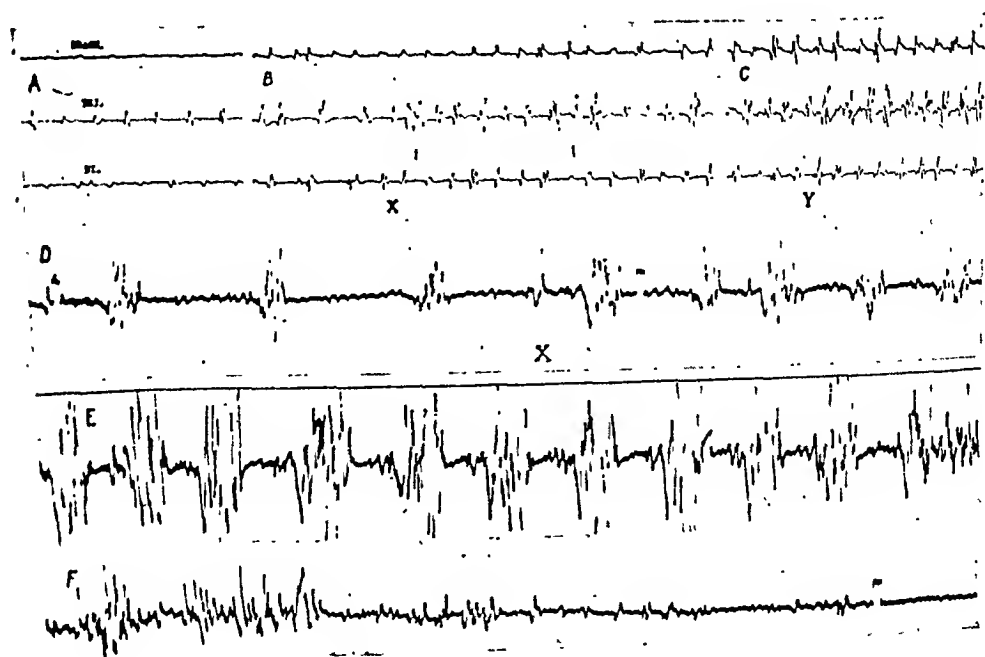


Fig. 7. PARALYSIS AGITANS. *A*, rest, biceps and triceps alternate, but with doubled beat in biceps. *B*, rest, biceps and triceps synchronous. Brachioradialis doubled frequency. *C*, synchronous beats in all muscles, plus doubling in triceps. *D*, shift single to double beat in all muscles. *E* to *K*, prolonged minimal flexion, lifting hand with elbow on support. *E*, 18th second, 5.5/sec. synchronous beats in biceps and brachioradialis. *F*, 26th second, shift alternate to synchronous. *G*, 32nd second, strength of flexion increased, triceps inhibited, brachioradialis frequency doubled. *H*, 36th second double spikes at tremor rate. *I*, 40th second, doubled frequency brachioradialis and biceps, diagonal lines indicate alternate beats. *J*, 52nd second, alternate beats dropped, single frequency, synchronous in all muscles. *K*, 62nd second, 2 seconds after relaxation, resting tremor as in *C*. No obvious reasons for changes in pattern.



to give a doubled frequency. These spikes increase in amplitude with increased effort to a value which may be as great as the amplitude of the original series. With still greater effort this doubled tremor may then pass over into a still more rapid series of well-synchronized spikes with no intervals of quiescence between tremor maxima (fig. 3E).

In other instances, normal and pathological, all trace of the previous tremor rate may be absent from such a spike series, except that it appears to be exactly a multiple of the previous tremor rate. Presumably the background of tremor impulses maintains the synchronization (fig. 5D and 7). Such a spike frequency of 25 per second might be slow enough to be detectable as a fine tremor, but at higher frequencies is effectively a smooth tetanus.

### *Reciprocal Character of Tremor*

This tremor of normal subjects is always simply alternating in biceps and triceps, the brachioradialis acting synchronously with the biceps. It seems to utilize the spinal mechanism of reciprocal inhibition. When the tremor is volitionally induced it takes on the clonic pattern such as appears in response to the stretch reflex of the decerebrate animal, or after pyramidal lesions in the human subject. This tremor also exhibits a second type of reciprocal action with reference to volitional rather than spinal reflex excitation. When stronger flexion is voluntarily performed, as for instance in lifting a weight as compared with free flexion of the elbow (fig. 2C as compared to A), the biceps tremor amplitude is increased, the triceps decreased. The spinal reflex type of reciprocal relation may then be designated as *clonic* reciprocal action; that accompanying voluntary motion as *tonic* or phasic is presumably assignable to the cortical level.

With extreme effort the clonic type of reciprocal relation may be overcome, to the extent that the biceps for instance (fig. 3E) may follow not only its own rhythmic beat but also be activated in phase with the triceps beat, resulting in an exactly doubled frequency. This appears to involve a reversal of biceps inhibition during triceps contraction, to a spread of excitation from triceps innervation to biceps.

These three phenomena, clonic and tonic reciprocal actions and the reversal of the clonic reciprocal to synchronous activation of opposing muscles, also appear in paralysis agitans and are illustrated in the following

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Fig. 8. PARALYSIS AGITANS. A, rest. B, start of voluntary tremor with 100 gm. weight in hand, at X, time in seconds. Instructed to increase effort at Y in C, rate and amplitude increase as in normal subjects. Resting tremor 4-5/sec. Voluntary tremor weak, 6.5/sec., stronger 7.5/sec. second which are values characteristic of normal subjects. D, oscillograph record of start of tremor at X in triceps of record B, 1 second between square wave signals. E, triceps during stronger effort of tremor which started above 7/sec., slowed to 6.5/sec. F, continuous with E, end of tremor.

figures. By the varying degrees to which they operate they largely determine the varieties in pattern manifest in pathological conditions. In addition to these three phenomena the reversal of *tonic* inhibition, not so far observed in volitional tremor, may appear in the spontaneous tremor of paralysis agitans. In this case, flexion for instance instead of decreasing the amplitude of tremor in the triceps increases it in both biceps and triceps, and the same may occur for extension. Such overflow of excitation, of voluntary activity in this case, to an opposing muscle is the counterpart of the usual reflex reaction to passive movement of the rigid patient, where again opposing muscles respond to stretch of either flexor or extensor by passive movement. The increase of periodic tremor amplitude in the opposing muscle in conditions in which, without tremor, tetanic contraction increases emphasizes again that tremor is a periodic form of contraction. Its intensity when present follows the usual pattern of tetanic contraction in voluntary activity and is subject to corresponding derangements of pattern.

While reversal of tonic inhibition in the volitional tremor of normal subjects has not been observed, its reversal in non-tremorous contraction with the extreme of volitional effort occurs frequently. That is, strong contraction against resistance may be accompanied by some degree of contraction in the opposing muscles. This is fundamentally the same type of overflow of activity as is seen in pathological rigidity, but occurs only with the extreme of effort—quite as volitional tremor is possible in the normal subject only during considerable exertion. One striking difference then between the manifestations of clonic and tonic reciprocal action, and their reversals, in normal and in pathological subjects lies in the level of effort at which they are elicited. These are reasons further justifying the schematic distribution of tremors with respect to the degree of effort as in figure 1. They also illustrate the thesis that many pathological motor phenomena can be viewed as accentuations or recombinations of the factors obvious in normal motor behavior.

### *Pathological Tremor Patterns*

In pathological tremors one finds derangement of the various components of which tremor consists independently of each other. In a simple alternating tremor of rest where both the flexors and extensors show complete quiescence between bursts, weak activity of either flexion or extension may completely abolish activity in the opposing muscle (fig. 4C and G). In cases liable to tremor or showing tremor in some muscles but no tremor in a given muscle at rest, voluntary activation of that muscle may appear as a clean tremor, with abolition of any tremor of rest in its antagonist.

Such cases, even though the tremor is evidence of pathological condition, may be said to have a normal *pattern* of tremor, in the sense that the clonic reciprocal factor acts as it does in the normal subject's voluntarily induced tremor, and that the tonic reciprocal factor acts on tremor amplitude as it does on the tetanic activity of voluntary movement. This normal or standard pattern, without implying that the tremor exhibiting it is a normal form of activity, may be taken as a basis of comparison for more complicated patterns of tremor.

There are two common deviations from this standard pattern that can best be understood as a degree of disorganization or modification of the two types of reciprocal activation and inhibition noted above. First, many cases of Parkinson's disease show a second series of bursts occasionally appearing one burst between each two of the usual series (fig. 5 and 7). This minor series is then exactly synchronized with the bursts in the opposing muscle. The minor series may slowly wax and wane in amplitude. At times the minor series may attain the amplitude of the major series, resulting in an exact doubling of the initial frequency. If two opposing muscles both perform in this manner, there occurs a doubled series of bursts in each muscle always synchronous with each other (fig. 6). Little or no tremorous movement then results, although a fine tremor can be felt in the muscles. In extreme cases this may be a persisting or nearly continuous condition with only occasional breaks to an alternating amplitude or to disappearance of the minor series. When such breaks occur, a period of gross tremor accompanies each of them. The phenomenon involves a reversal of clonic reciprocal inhibition to a spread of excitation to opposing muscles.

The other form of deviation from normal reciprocity, in this case that of the tonic type, is seen in certain Parkinson cases in which movement does not decrease tremor in either of the two opposing muscles. The amount of force exerted in the motion is measurable as the *increase* of the tremor in the voluntarily activated muscle in spite of the failure of its opponent to relax, and this situation corresponds to the rigidity of non-tremorous Parkinson motion (fig. 6). Part of this apparent weakness of such motion is then assignable to failure of the opponent to relax, in addition to whatever essential paralysis may exist.

Another variety of this derangement of tonic reciprocal action is seen in pairs of muscles which, although undergoing simple or undoubled tremorous contraction, do so synchronously; that is, flexor and extensor tremor bursts coincide and tremorous motion may be at a minimum or absent (fig. 6). This appears to indicate first a complete absence or suppression of clonic reciprocal relations, both opposing muscles responding to the same

periodic drive. Such cases then may or may not show tonic reciprocal inhibition on voluntary effort, indicating again the independence of these two mechanisms of reciprocal action. In spinal ankle clonus it is often found that the tibialis anterior and gastrocnemius contract in synchronous bursts at a frequency of 6 to 8 per second, in response to stretch of the gastrocnemius, under reflex instead of volitional activation.

### *Relation of Pathological Tremor to Effort*

Contrary to the usual statement that the tremor of paralysis agitans is a tremor of rest, in a majority of cases the tremor continues during a considerable degree of voluntary effort in the contracting muscles. It may be reduced or suppressed in the antagonist to the contracting muscle; that is, the tremor may be reciprocally inhibited quite as a normal continuous contraction is. The tremor is overlaid and more or less obscured in some cases by the addition of tetanic contraction of voluntary activity. However, in certain more severe cases nothing but tremor bursts occur in contracting muscles; in fact, the contraction is performed almost entirely by a succession of twitches (cogwheeling). The tremor becomes in short a tremor of action. In general the tremor is affected by passive movement, posture, voluntary effort, etc., somewhat as is normal activity (fig. 5); that is, reciprocal inhibition of tremor in one muscle occurs in response not only to reflex or voluntary initiation of activity in its antagonist, but in response to changes in posture that involve contraction to achieve or to maintain. Such contraction itself may consist of tremor. When tremor is obscured by voluntary tetanus, as in lifting a weight, the tremor often reappears while holding the lifted weight and becomes still more marked during slow relaxation. In fact, slow relaxation after a contraction is a means of making any tremor tendency more overt (fig. 4D).

Usually the tremor of Parkinson's disease can be inhibited or relaxed transiently by voluntary attention or conscious intention, or by passive movement, as it may be nearly or completely obliterated at the cessation of effort. It then reappears after a few seconds. Presumably the conscious attention to termination of voluntary activity is equivalent to conscious intention to suppress the tremor during rest. On the other hand, any disturbance resulting in 'nervous' tension or excitement, anxiety, confusion, etc., increases the tremor. In other words; there may be a nervous or psychic component of tremor which acts parallel to voluntary effort to contract muscles and is comparable to the involuntary activity of rigidity. This component could be represented along the base line of figure 1; relaxation of such tension to be measured toward the left and increase of tension, toward the right.

In the combination of muscles usually recorded in our tests, biceps, triceps and brachioradialis, the triceps seems to be more prone to tremor than the biceps, especially in the partially flexed position which accentuates tremor of the arm in general. The brachioradialis is typically synchronous with the biceps, although one of the commonest variants is for this muscle to shift in synchronism from biceps to triceps rhythm, or to follow both rhythms, i.e., to exhibit a doubled frequency. This can often be induced by changes in posture, or may happen during apparently constant conditions. The same phenomena discussed above appear in other forearm muscles, and in those of the legs and of the neck; the doubling of frequency in a given muscle, occurring in normal subjects only under critical conditions, is not infrequent in our pathological cases. It appears to represent a disorganization of pattern of reciprocal inhibition in general.

As indicated above, the form of the Parkinson tremor and its pattern of distribution in various muscles involved, and the effect on it of reflex, passive and voluntary movement so resemble the phenomena that can be purposively induced in normal subjects as to suggest that the mechanisms are the same however differently set into activity. That is, the Parkinson tremor seems to involve a mechanism normally present but abnormally activated or released. In the normal subject where considerable tension is required to induce tremor, its easier maintenance once started may be assigned to reciprocally acting stretch reflexes, as in clonus. In the case of paralysis agitans, however, under conditions of relaxation the tremor may appear and disappear without any contraction other than periodic tremor bursts being present. The fact that the lesion of this disease is in the brainstem or above it, as well as the fact that the tremor may appear without any previous peripheral activity to set up stretch reflexes, suggests an initiating periodic activity in higher centers. However, as the tremor appears after a period of quiescence it tends to build up progressively as if each tremor contraction reflexly reinforced the succeeding one; and conversely the patient will often be able to reduce the tremor by sitting on or otherwise immobilizing the hand. Therefore, whatever the initiating cause, stretch reflex impulses set off by each tremor burst help to maintain it; that is, any tremor presumably has a spinal clonic component. This connotes a hypersensitivity of the spinal level to stretch stimuli, presumably assignable to release of inhibition from higher levels by the degenerative processes of the disease.

This release of lower centers is also consistent with two other factors characteristic of paralysis agitans; with some degree of voluntary paralysis, and with the overactivity appearing as rigidity. In general the removal of the influence of a higher level over a lower is liable to appear as release of the



lower center from inhibition—as in the extreme case of decerebration—as well as in release from or removal of a more highly organized pattern of activity such as paralysis of voluntary movement with hyperactivity of reflex movement. Although rigidity is usually detected clinically as resistance to passive movement, it appears without passive movement in myographic records as tonic involuntary contraction, often of both flexors and extensors. In fact, the resting tremor can be viewed as a form of rigidity that is intermittent, or periodically inhibited, in a reciprocal alternation between flexors and extensors (2). As a variant of this, one often finds a tremor periodicity in one muscle, balanced against a tonic rigidity in its opponent so that the limb vibrates with a reciprocating tremor but still without overall displacement. Change of posture may then convert the tonic activity of the rigid muscle into a clonic tremor.

### *Components of Tremor Activity*

The usual electromyogram duplicates clinical examination, if more quantitatively, not necessarily more significantly because of so many factors, state of nervous tension, voluntary or semi-voluntary effort to resist or to assist the test on the part of the patient, etc. These factors complicate both methods of examination, and thus tend to make them equally equivocal and dependent on the judgment of the observer as to the total state of the subject. Consideration of tremor, whether involuntary, voluntary or induced by such an agent as adrenalin has an advantage that, while this is more or less affected by voluntary effort as to overall presence or absence like normal voluntary contraction; it is not so readily modifiable by the subject as to such details of pattern as discussed above. The pattern of tremorous motion, considered as an aspect of movement, promises to offer a means when its mechanisms are better understood of testing these mechanisms more or less independently of the subject's interference, as compared for instance to active voluntary or passive movement or conditions of presumed 'rest'. Its study both in normal human subjects, in pathological cases and by means of animal experiments therefore seems to offer promise not only for the analysis of nervous system action in general, but for a more critical diagnostic aid in testing for certain pathological conditions.

The typical tremor pattern may then be analysed into several components or *factors* and different patterns of tremor may be described in terms of the interactions of these factors with different relative intensities and degrees of abnormality or disorganization. These factors out of which the tremor pattern is constituted seem to be recognizable as follows:

a) Excitation to contraction, voluntary or involuntary; tremor is after all a form of action. In this sense all tremors are action tremors, the real distinction being whether the action is volitional or not.

b) A periodic function; some (presumably spinal clonic) mechanism normally suppressed or not operative breaks up the contraction of rigidity or of voluntary effort into brief intermittent periods of action; possibly periodic inhibitory action occurs.

c) Reflex clonic reinforcement of periodic activity, assignable to stretch stimuli.

d) Clonic reciprocal action, resulting in alternate activation of opposing muscles.

e) Tonic reciprocal inhibition of antagonists in voluntary effort, applying to tremor activity as to normal movement.

f) Reversal of clonic reciprocal action with spread of excitation to opposing muscles, resulting in synchronous tremor.

g) Replacement of tonic reciprocal action by simultaneous excitation of antagonists, corresponding in terms of volitional activation to reflex rigidity.

h) Nervous tension, anxiety, etc., reacting on the contractile function but affecting also periodic activity, making tremor more pronounced. Certain excitant drugs duplicate this effect without pathological derangement.

### *Criteria of Pathological States as Inferred from the Pattern of Tremor*

These may be discussed in terms of the phenomena of paralysis agitans but seem to apply to other conditions involving tremor. Criteria may be designated as follows:

a) *Frequency of Spontaneous Tremor.* The voluntary tremor of normal subjects at 6 to 8 per second is taken as a standard. While it is not conclusive that the mechanisms involved are precisely the same in all cases, the fact that familial tremors, clonus, tremor induced by adrenalin or excitement, and tremors of advancing age, in otherwise normal subjects, fall in this 'normal' range justify this as a standard. We have found rates of 3 to 7 per second in different cases diagnosed on the basis of the total picture as paralysis agitans but it is not clear that the rate is a straightforward measure of the severity of the overall condition, for the pattern of paralysis agitans is variable and complex.

b) *Ability to Induce Tremor Voluntarily.* Some cases of paralysis agitans with a spontaneous tremor as low as 4 per second have been able to induce voluntarily a regular reciprocal tremor of 8 per second. No trace of a 4 per second tremor may remain in such instances. When a voluntary tremor is successfully accomplished the pattern tends to become 'normal', i.e., regularly reciprocal in opposing muscles whatever the abnormality of pattern of the spontaneous tremor. Inability to induce such a normal pattern is a measure of the involvement of voluntary control. Short of this, many cases of paralysis agitans can increase or decrease the amplitude of spontaneous tremor by conscious intent.

c) *Increase of Rate of Tremor with Voluntary Activity.* Apparently the more severe the deterioration in general, particularly as to paralysis, the less does rate increase with increase of voluntary effort.

b) *Abolition or Obscuring of Tremor by Steady Tetanus with Increase of Activity.* Persistence of tremor through strong effort seems not to correlate well with the other symptoms of paralysis agitans; as if the tendency to tremorous activity or to periodicity of contraction were a relatively independent entity. This point of view is supported by the readiness with which many normal persons exhibit tremor with relatively slight stress.

c) *Tonic Abolition of Tremor of an Antagonist in Voluntary Motion.* Failure of such inhibition is the periodic counterpart of rigidity. Its presence is an indication of the normal reciprocal inhibition characteristic of voluntary activity, but acting here on the periodic activity of tremor.

f) *Alternate or Reciprocal Involvement of Opposing Muscles in the Tremor at Rest or During Weak Voluntary Effort.* Failure of such clonic reciprocal action is of very common occurrence in Parkinson's disease, and not usually seen in familial, excitement, adrenalin and senile tremors of mild degree, or in the voluntary tremors of normal subjects, or in the voluntary tremors of Parkinson cases capable of inducing an increased rate of tremor comparable to the normal subject. The two conditions, synchronous doubled frequency and synchronous single frequency, are not usually observed in the same case, and the first is of less common occurrence than the second. The significance of these phenomena for diagnosis of the pathology involved may not become clear without reproduction of the conditions in animal experiments. It may be pertinent to consider that this type of pattern also occurs in voluntary tremor of normal subjects on extreme effort, and in some cases of clonus after spinal section or severe damage to the pyramidal system. For instance, ankle clonus induced by stretch of the gastrocnemius may involve the tibialis anterior in tremor pulses synchronous with those of the gastrocnemius.

In the comparison of the tremor patterns of paralysis agitans with those of other pathological states diagnosed differently, or not conclusively diagnosed, we have found enough of the same variations from the pattern we have taken as standard here to indicate that there is not any one definite pattern characteristic specifically of paralysis agitans. Rather, it appears that many pathological conditions may involve variations in nervous function which in turn modify tremor pattern when tremor is present at all. In our limited experience so far with these various conditions it appears that the Parkinson condition exhibits a greater variety of pattern, and more frequent and complex deviations from the standard pattern, than do most other conditions. This question is being followed further as opportunity offers.

## DISCUSSION

The object of comparing these tremors of various causation but of common forms has been to see how much they have in common. All these periodic activities seem to have a common component of spinal clonus, as discussed by Hofer and Putnam (3) which reinforces any periodicity initiated elsewhere and perhaps even controls its basic pattern. Further they all are subject in some degree to the same variations in pattern, the tremor of paralysis agitans being the most variable.

The lesion of paralysis agitans is generally agreed to be specifically in the upper brain stem (4) and to be degenerative in character. The production of tremor in animals by specifically placed surgical lesions in this region (5) and the absence of tremor after various other partial or complete decerebrations confirms this. The appearance of tremor as a form of *overaction* (tremor of 'rest' accompanied by or associated with rigidity under conditions where the normal shows no activity) has suggested a release of motor function from some higher control, and the accompanying paralysis points to the

defect again as involving a decrement in the higher levels of function. The picture then is that of overactivity of some component of movement control involving the brainstem and transmitted to the spinal level where it alters the pattern either of voluntary or of reflex movement.

The overt pattern of muscular activity obviously reflects the pattern of ventral horn cell discharge and this in turn is immediately influenced by the activity of the internuncial pool at the spinal level. Whatever the lesion or the disorganization of pattern at higher levels of function in pathological cases, the final synthesis of the pattern of response must be due to the summation or the resultant of all the influences that play upon the spinal level. This level seems to be so prone to express itself in the pattern of clonic tremor that a variety of factors permit its release. The question might then be raised whether lesions which affect one or another component of activation of the spinal level result in periodic discharge from the higher centers themselves, or only permit the characteristic clonic pattern of the spinal level to emerge.

The idea that clonic tremor is fundamentally a primitive cord pattern released by degeneration in higher pathways, suggested by Kinnear Wilson, has been repeatedly called in question as being inadequate at least. Benda and Cobb (4) add to this the concept that activation of the pyramidal system tends to result in phasic activity, while the extrapyramidal system tends to maintain random or tonic activity. Degeneration in the extrapyramidal system then leaves the pyramidal system in uncompensated influence on a cord level itself inclined to respond phasically. Hoefler and Putnam (2) propose a trigger action, assignable to the pyramidal system which sets off the clonic alternating activity of tremor inherent in the cord mechanism.

It has been shown by Putnam (6) that section of the corticospinal tract may abolish the tremor of paralysis agitans, and by Bucy (7) that ablation of the pyramidal motor cortex will also reduce or abolish tremor, although in most cases more or less voluntary paralysis appears to accompany the suppression of the tremor. On the other hand voluntary paralysis associated with pronounced tremor is the typical picture to which the term paralysis agitans is appropriate. It has not been demonstrated that bursts of activity at a tremor rate occur in the pyramidal tract during tremor, and Schwab and Cobb (8) found no correlation between cortical electrical activity and Parkinson tremor rate. The latter finding is not too critical, since the spontaneous activity of the electroencephalogram is most definitely rhythmic at rest and activity dissipates its pattern, and the activity represented by the alpha sequence is presumably not that which initiates activity peripherally (9). The electrical bursts accompanying convulsive activity are indeed accompanied by pyramidal tract potentials which might activate

the cord to motor response (10) but such motor convulsions are possible after section of the pyramidal tracts (11) and not when these only are left intact. The convulsive electrical activity of the cortex however is presumably not assignable to the same cortical mechanism as is the spontaneous activity of rest.

Mettler and Mettler find that phasic activity results from cortical stimulation when only the pyramidal system is left intact at the brain stem level, but is converted to tonic activity by even minor interference with the pyramidal tract, and that the dorsal root afferent supply is necessary for such phasic activity. On the other hand, Pollock and Davis (12) found that Parkinson tremor was not abolished by root section, although its rate and regularity were modified, and it may be questioned to what extent the evidence from phasic activity following cortical stimulation may apply to the clonic activity of specific alternating tremor.

Since section of the extrapyramidal system does not abolish convulsive phasic activity, and since destruction of the pyramidal system does and since the latter procedure abolishes tremor, Bucy (13) infers that a circuit operates from motor cortex to midbrain and back through the extrapyramidal system to the cortex whose normal function is to prevent periodic cortical discharge. The lesion of paralysis agitans then breaks this circuit and permits the cortex to respond in its own essential rhythm. This is then impressed upon the cord motor system via the pyramidal tracts, to emerge as tremor of rest. A similar tremor of action is accounted for by a circuit involving the cerebellum. This hypothesis again involves the concept of a release, here at the cortical instead of the spinal level. This concept might also be employed to account for rigidity without tremor, with appropriate inferences as to the various actions of such circuits (14).

Since the cerebellar intention tremors can be sharply differentiated from tremors of rest, and also from those tremors of action which resemble Parkinson tremor in form and occur in many pathological conditions, a difference should be emphasized between clonic tremors of rest or of action whose pattern is in general that of cord clonus, and those intention tremors which consist essentially of ataxic over- and undershooting manifest chiefly at the end of movement and associated with efforts involving precision of attainment as the intention factor. The Parkinson tremor which often carries over into a very considerable degree of voluntary movement, or familial tremor or others resembling these in form do not have this specific intention component, nor do they differ in other manifestations from the tremor of 'rest'. The tremor of rest is itself activity, and the designation of it as resting only refers to the lack of voluntary effort involved. To include such tremors of rest and of action in a common category only involves the in-

ference that as far as the tremor is concerned, the involuntary activity of rigidity is equivalent to the voluntary activity of effort.

The origin of rhythmic action in general is not difficult to picture, as the result of mutual facilitation in neurones spontaneously or tonically activated, such that they tend to fall in phase with each other. This is in fact equivalent to spatial summation. Such an explanation is the one usually offered for the rhythmicity of the electroencephalogram and its disappearance with activity is apparently chiefly a matter of desynchronization by random activation from other sources. An experimental demonstration of the distribution of potentially rhythmic and synchronous activity into continuous activity has been presented for the optic cortex by Bartley (15).

The optic cortex of the rabbit, the alpha rhythm of which has a frequency of 4 to 6 per second, may be conveniently stimulated with synchronized volleys of impulses set up by single shocks to the optic nerve. The response to each shock is a brief series of impulses, followed after an interval by one or more alpha waves. If a second shock is now applied at the crest of an alpha wave its volley of impulses finds the optic cortex sensitive, and a second alpha wave follows. If the shock falls in the trough following an alpha wave little or no response occurs, the cortex being relatively insensitive at that phase of the cycle. If now repetitive shocks at twice the alpha frequency are delivered to the nerve, at first every other shock is effective and the cortex is driven at the alpha frequency; but soon the alpha responding elements redistribute, some following one shock and some the succeeding shock at half the alpha period, so that two alternate trains of alpha waves result, with a doubled overall frequency. The frequency can be doubled again by increasing the shock frequency to four times the normal alpha rate, and finally to eight times, whereupon each wave becomes so low and overlaps its neighbors to such a degree that the potential line is quite flat. Activity has become continuous instead of periodic, but by employing elements in rotation to attain a higher overall frequency than any one is capable of. Stimulation of the retina by light appears to accomplish the same result, by sending to the cortex a continuous barrage of impulses which desynchronizes the nervous elements of the alpha process.

This tendency to synchronization of nerve elements acting in parallel is a general one in the nervous system; and it is generally opposed by the random character of the impulse stream received from other parts of the nervous system or from sensory stimulation. The spinal cord often exhibits synchronization of ventral horn cell discharge during voluntary activity in certain pathological states (for instance some cases of multiple sclerosis or other cord damage) as contrasted to the normal tetanus which consists of a random discharge of neuromotor units. The frequency achieved in these cases, 10 to 30 per second or more, may be too high to give overt motor tremor, but it is no less a periodic rather than a continuous activity, and probably represents the rate of discharge of each of many motor neurones, all neurones of a group acting approximately in phase.

An analysis of the fundamental mechanism of clonus, not necessarily alternating but applicable to one muscle group, has been offered by Denny-Brown (16). An essential phenomenon is the tendency to synchronism in parallel ventral horn cells, presumably by mutual facilitation or excitation.

When so discharged in synchronism, say by an abrupt stretch stimulus, a silent period follows, comparable to the interval that occurs between the first twitch of a knee jerk and a following more complicated discharge. This permits the muscle to relax, whereupon continuing stretch restimulates its afferent endings. Stimulation of stretch afferents by active contraction, in addition to passive stretch, may account for reflex inhibition of the opposing muscles. Reciprocal innervation at the cord level, plus the mechanical stretching of an opposing muscle by contraction of the muscle initially stimulated, will account for alternating clonus; overflow of excitation from one muscle center to the other would be required to account for synchronous clonus in opposing muscles, often observed in pathological and in apparently normal subjects.

Until periodic discharges from the motor cortex over the pyramidal tracts can be demonstrated as the pacemaker of tremor, it is perhaps not necessary to infer them. An alternative is to infer that a modification of the total pattern of pyramidal discharge to the cord level so alters the state of the internuncial system that clonic activity results. It is not necessary to infer that this is a primitive pattern; rather it may be viewed as a manifestation of such normal cord functional components as stretch reflex action, reciprocal innervation, spread of excitation, etc., which are normally useful in other actions than tremor, but which result in tremor when the balance of normal forces acting at the cord level is altered. The pattern of voluntary movement is imposed on this complex of cord functions via the pyramidal and other tracts, and this pattern must normally involve both activation and suppression at the cord level; an example would seem to be the tonic depression of tremor amplitude in one muscle when its antagonist is voluntarily activated.

It appears that the higher levels of the nervous system not only specifically excite the cord level to activity expressed as muscular motion, but also set up a pattern of excitability on which peripherally arising reflexes act. The presence of a constant pyramidal discharge to the cord during rest (17, 18), which must be increased above the resting level to induce overt movement, obviously represents a tonic influence maintaining a 'resting' state of excitability involving both degree and pattern of distribution. Tonic discharges from other centers presumably add their influence into the normal resting pattern of excitability. When these tonic stabilizing influences are removed, or altered, as by decerebration or disease, the cord acts in a pattern depending on what influences still persist. Similarly the motor cortex, as a regulator of spinal action, is itself regulated by other centers, of which the brain stem level seems to be a critical one with reference to tremor. In a system so altered as to be prone to tremor, for instance in such cases of

paralysis agitans as show reappearance of tremor after its voluntary suppression and without specific stretch stimuli as required for spinal clonus; the phasic activity noted by Mettler and Mettler (11) to be present when only the pyramidal tracts remain intact might be adequate to initiate periodic cord function, even if the phasic discharges were not of the frequency characteristic of spinal clonus. Phasic waxing and waning of tremor of rest which occurs in paralysis agitans might also be accounted for in this manner.

It has been repeatedly noted that the pyramidal system, though obviously involved in tremor, may not itself be the seat of degeneration, and the pyramidal tracts must be intact for certain tremors to be manifested. However, it is also recognized that voluntary activity is very much impaired in Parkinson's disease to the extent of considerable paralysis. This apparent discrepancy is not a serious one. Any conception of the pyramidal system as the source of 'voluntary' activity overlooks the fact that the motor cortex must itself be activated, by other cortex, and under the conditioning or patterning influence of the extrapyramidal system, etc. That the pyramidal system is intact, even if it be the major pathway for voluntary activity, does not mean that it acts normally on the cord, either in terms of patterning the cord excitability to reflex stimuli or in terms of specific excitation to motor activity. The variations in pattern of tremor considered above may be looked upon as variations in the patterning of cord excitability by an abnormally acting pyramidal system, the degree and character of the abnormality depending on the extent and location of lesions whose altered activity is reflected to the motor cortex. This corresponds to Bucy's conception of the involvement of the motor cortex by lesions in the midbrain, even without his inference that the motor cortex originates the periodic activity that results in tremor.

That the effect of voluntary activity on the pattern of tremor should then tend to follow the mode of voluntary activity itself, as if the tremor in simple cases were essentially merely a periodic form of otherwise normal contraction, is reasonable enough. It is also reasonable that variations in pattern from the simple clonic alternating form should be looked upon as manifestations of variations in the patterning of voluntary movement. In a real sense the abnormal functioning of higher centers is reflected on the cord level to make its pattern of activity correspondingly defective or abnormal. This relation is illustrated by the condition of rigidity; the response to passive movement is here a spinal reflex response, under an abnormal state of excitability that permits stretch of one set of muscles to activate also the opposing muscles, without the normal operation of reciprocal inhibition. When clonic modulation is superposed on this abnormal cord functioning, cogwheeling results as a summation of overaction plus tremor; the overaction of rigidity becomes periodic instead of tonic.



An approach to the further analysis of tremor mechanisms might be to look for specific nervous system actions that would permit the restatement of these generalities in more specific terms than are permissible at present. Such studies as those of Lloyd (19, 20) a third of which is cited above, and of Bernhard and Therman (21, 22) are most pertinent in this direction.

#### SUMMARY

The tremor pattern of various pathological conditions exhibits a range of variation which suggests that any given pattern results from the summation of a number of factors or physiological components, added together in variable amounts or intensities. The components into which pathological tremors can be analysed can also be recognized in the volitional tremor induced by clenching the muscles of the arm and voluntarily initiating a rapid alternating or reciprocating movement. The same components may be identified as the physiological components of normal movement, involved in different combinations as the periodic activity of tremor.

Tremor itself may therefore be looked upon as a periodic form of movement, and in many respects its change in pattern with volitional effort follows the rules of voluntary or reflex movement patterns. The manifestations of tremor are those of muscles directly reflecting the activity of the spinal level, while the ultimate occasion of the occurrence of tremor is typically a lesion above the spinal level. The pathological disorganization then is reflected to the otherwise normal spinal level by a change in the tonic influence of the higher centers mediated over the pyramidal or extrapyramidal systems.

The fundamental pattern of alternating tremor, including spinal clonus, is apparently inherent in the spinal level of function, although the activity of its physiological components is normally expressed in terms of normal motor movement. It may be looked upon as a release phenomenon, but presumably not as a release of any archaic or primitive pattern of movement. Rather it is the manifestation of a pattern resulting from reflex or volitional activity when certain components normally preventing tremorous expression are more or less deranged or suppressed.

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## *Sensitivity of the Respiratory Center to Anemic Hypoxia*

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WHETHER THE RESPIRATORY center can be directly stimulated by hypoxia has not been conclusively proven.<sup>2</sup> After denervation of chemoreceptors, experiments conducted for the most part under anesthesia have shown no response by the respiratory center to hypoxia; the center's sensitivity was possibly impaired by anesthesia. On the other hand, a positive response to hypoxia in denervated animals might either be attributed to the existence of unknown chemoreceptors or to a nervous path which regenerated after chronic denervation.

Carbon monoxide, methemoglobin and anemia afford an opportunity to study the center's sensitivity to hypoxia in men and unanesthetized animals, since maintenance of normal arterial oxygen pressure precludes any abnormal stimulation of arterial chemoreceptors, and diminished oxygen arterial content, through loss of available hemoglobin, produces a fall of oxygen pressure at the respiratory center. Studies of respiratory responses to acute carbon monoxide hypoxia have been made in men and unanesthetized dogs (1, 2), and to the methemoglobin hypoxia in unanesthetized dogs (3).

Even though ventilation of anemic patients has been recorded (4, 5) no attempt was made to prove hyperventilation was produced by hypoxia, although this mechanism has been taken for granted frequently. We therefore planned to study circulatory and respiratory adjustments in anemic patients breathing room air and 100 per cent oxygen to see whether the greater volume of oxygen dissolved in the blood would relieve tissues of oxygen want and eliminate hypoxic hyperventilation.

Nine anemic patients were studied under experimental conditions and methods similar to those described in a previous paper (6).

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<sup>2</sup> For a complete review of the subject, see: Gesell, R., *Ann. Rev. of Physiol.* 1: 185, 1939; Schmidt, C., *Ann. Rev. of Physiol.* 7: 230, 1945; Bernthal, C., *Ann. Rev. of Physiol.* 6: 155, 1944; and Björstedt, A. G. H., *Acta Physiol. Scand.* 12: supp. XXXVIII.

## RESULTS

*Pulmonary Ventilation.* Ventilation measurements made in four patients throughout recovery of anemia are presented in table 1. Two patients (*A. S.* and *J. M.*) had pernicious anemia and two (*A. T.* and *D. G.*) hemorrhagic anemia. While anemic, two patients presented a 20 per cent

TABLE 1. OXYGEN BREATHING EFFECT ON RECOVERING ANEMIC PATIENTS

CASE	Hb	VENTILATION <sup>1</sup>		PULSE RATE		O <sub>2</sub> /USED IN AIR	B.M.R.	O <sub>2</sub> VENTIL. EQUIVAL.	CO <sub>2</sub> VENTIL. EQUIVAL.	R.Q. IN AIR
		In air	In O <sub>2</sub>	In air	In O <sub>2</sub>					
	g. %	l/min.	l/min.			l/min.	%	l/min.	l/min.	
<i>A. S.</i>	4.5	7.3	9.5	84	71	0.215	+5.1	27.6	34.3	0.80
	5.3	7.2	8.8	82	66	.				
	7.2	6.6	7.9	69	58	0.210		25.9	33.6	0.77
	8.8 <sup>1</sup>	6.9	7.9	59	54	0.192	-5.3	29.8	32.3	0.92
	11.9 <sup>1</sup>	27.	7.6	67	58					
	13.0 <sup>1</sup>	7.0	7.2	56	52					
	12.5	6.3	6.8	57	51					
	16.4	6.1	6.1	55	50	0.198	-11.3	25.3	30.2	0.83
<i>J. M.</i>	8.2	9.4	11.2	84	72	0.254	+19.4	30.7	36.5	0.84
	10.0	9.5	10.0	83	70	0.260		29.9	33.4	0.89
	12.6	9.1	9.9	76	68	0.233		32.5	36.2	0.89
	12.8	8.4	9.4	79	72	0.237		29.1	33.1	0.87
	14.5	8.1	8.6	75	68	0.237		28.3	34.2	0.83
	13.8	8.2	8.2	71	65	0.210		30.6	33.6	0.90
	15.4	7.8	8.2	73	66	0.204	+3.2	32.0	32.6	0.98
<i>A. T.</i>	5.2 <sup>1</sup>	6.8	7.6	82	65	0.234	+5.7	24.3	32.0	0.76
	11.2 <sup>1</sup>	6.1	6.1	69	65	0.216	-1.1	23.3	28.0	0.81
<i>D. G.</i>	8.7	6.5	7.7	68	61	0.244	-8.2	22.1	31.1	0.71
	—	6.7	8.2	72	66	0.252	+1.1	22.1	25.3	0.87
	12.8	6.6	8.1	71	66	.				

<sup>1</sup> As determined by O<sub>2</sub> capacity. Other determinations with a Zeiss-Ikon hemoglobinometer.

<sup>2</sup> At 37°C., complete saturation and prevailing barometric pressure.

increase in ventilation and one an 11 per cent increase; no change was noted in the fourth case. Values were compared with those obtained at normal hemoglobin levels.

Ventilation values per square meter of body surface of the whole anemic group were found significantly higher ( $4.8 \pm 0.32$ ) than in normal individuals ( $3.65 \pm 0.09$ ). Ventilation of normal subjects was measured in the sitting posture, in which position normal lung ventilation increases. Ventilation

was measured in recumbent anemic patients and the difference in ventilation values became, for that reason, still more significant.

Oxygen consumption increased during anemia, as compared with values obtained at normal hemoglobin levels of those patients. Carbon dioxide production was not increased in the same proportion as that of oxygen consumption; a fall of the R.Q. resulted.

TABLE 2. OXYGEN BREATHING EFFECT ON VENTILATION AND PULSE RATE OF ANEMIC PATIENTS

CASE	TOTAL Hb CAPACITY	LUNG VENTILATION <sup>1</sup>				O <sub>2</sub> VENTIL. EQUIVAL.	PULSE RATE	
		In air	In O <sub>2</sub>	O <sub>2</sub> -air in % air	In air per sq. m.		In air	In O <sub>2</sub>
	vol. %	l/min.	l/min.		l/min.	l/min.		
L. L.	4.8	8.9	9.7	9.0	5.04	30.2	76	64
F. O. C.	8.0	8.4	10.9	29.8	6.24	22.5	88	79
S. G.	11.9	5.4	—	—	3.47	—	70	—
A. M. C.	12.2	6.5	7.7	18.5	5.07	27.1	69	56
		6.6	7.4	12.1	5.12	—	71	57
S. P.	9.1	6.8	7.4	8.8	4.14	32.7	71	62
		7.1	7.7	8.5	4.37	—	64	56
A. T.	7.0	7.3	8.2	12.3	4.62	24.3	82	65
A. S.	6.0	7.2	9.2	27.8	4.29	27.6	78	67
J. M.	11.0	9.4	11.2	19.2	6.18	30.7	84	72
D. G.	11.7	6.5	7.7	18.5	3.51	22.1	68	61
Average.....				16.4	4.76 ± 0.32 S.D. ± 1.0	27.1 ± 1.5 S.D. ± 3.9		

<sup>1</sup> At 37°C., complete saturation and prevailing barometric pressure.

The average oxygen equivalent was  $27.1 \pm 1.5$  in the 9 anemic patients (table 2), an increase over the average value of  $22.8 \pm 0.63$  in 21 normal individuals. In the 4 anemic subjects presented in table 1 the oxygen equivalent was nearly the same under both anemic and normal conditions. The CO<sub>2</sub> ventilatory equivalent was clearly increased during anemia. Addition of 4 per cent of CO<sub>2</sub> to the inspired air of 5 anemic patients produced an average ventilatory increase of 133 per cent. In normal patients, Shock and Soley (7) observed an average increase of 100 per cent.

In the most severe stage of anemia, inhalation of 100 per cent oxygen produced an average increase in ventilation of 16.4 per cent over ventilation in air (table 2). This average approximates the value of 13.6 per cent found in 50 healthy subjects by Shock and Soley (8, 9) and of about 20 per cent found by Edelman, Whitehorn and Hitchcock (10). However, it can be seen in table 1 that in 3 of 4 subjects followed until recovery, increase of ventilation by oxygen breathing was greater at low hemoglobin levels than at normal or almost normal levels.

*Oxihemoglobin Dissociation Curve.* Oxygen pressure at the half-saturation point, pH 7.4 and 37°C., shifted to the right in two anemic patients; oxygen pressures were 31 and 27 mm. Hg. These values should be compared with the average normal of 25.4 mm. calculated from literature data and from our results in three healthy men. In the third case, an erythroblastic anemia, the shift was left of the normal curve. Dill *et al.* (11) noted a similar displacement of the dissociation curve in a typical case of pernicious anemia.

TABLE 3. BLOOD CHARACTERISTICS RECORDED FOR CERTAIN ANEMIC PATIENTS

CASE	HbO <sub>2</sub> CAPACITY	ARTERIAL SATURATION	T <sub>50</sub> <sup>1</sup> OF BLOOD	T <sub>50</sub> <sup>2</sup> OF PLASMA	TOTAL CO <sub>2</sub> OF BLOOD	ARTERIAL pCO <sub>2</sub>	ALVEOLAR pCO <sub>2</sub>	ARTERIAL pH <sub>a</sub>	CALCULATED pH <sub>s</sub> OF MIXED VENOUS BLOOD
	vol. %	%	vol. %	vol. %	vol. %	mm. Hg			
L. L.	4.8	97.7	50.0	52.6	48.2	34.5	—	7.40	7.37
F. O. C.	8.0	100.0	49.8	54.0	49.8	40.0	—	7.37	7.34
A. T.	7.0	90.7 <sup>3</sup>	52.7	56.8	54.2	44.0	37.9	7.36	—
	15.0 <sup>1</sup>	95.4	46.3	53.4	48.0	44.0	38.5	7.34	—
S. G.	11.9	93.8	49.7	55.9	51.0	42.8	—	7.37	—
A. M. C.	12.2	94.6	52.6	59.6	55.1	46.0	38.2	7.38	7.34
S. P.	9.1	95.1	50.0	54.7	48.8	36.0	34.8	7.42	7.39
Average.....		95.3	50.8	55.6	—	40.6	—	7.38	—

<sup>1</sup> Patient recovered, data not included in average.

<sup>2</sup> Small clot in arterial blood.

<sup>3</sup> Total CO<sub>2</sub> content at complete O<sub>2</sub> saturation and pCO<sub>2</sub> equal to 40 mm. Hg.

The pO<sub>2</sub> of the half-saturation point at the pH of the arterial serum differed very little from that at pH 7.4, since in anemic patients the pH of arterial serum was not far from the standard value of 7.4.

*Arterial Hemoglobin Saturation.* Average and all individual values but two fell within normal values given for the tonometer technic. Of two cases outside normal range, the results of one, showing a 100 per cent saturation, might be explained by the red cells' high sedimentation rate, which made good duplicate analysis difficult; the other resulting figure of 90.7 might be due to a small clot in the arterial blood used for oxygen content determinations.

As stated in a previous paper (12) we considered that figures given by tonometer technic for arterial oxygen saturation should be compared only with normal values obtained by a similar method, since recent investigations have shown that such results were too low. Thus we do not give absolute oxygen pressures calculated from the arterial saturation and the hemoglobin dissociation curve in anemic patients; pressures were found normal with the method used.

*Arterial Carbon Dioxide and pH.* In 6 anemic patients the average alkaline reserve<sup>3</sup> (table 3) for whole blood was 50.8 volumes per cent, with a range from 49.8 to 52.7; the average for plasma was 55.6 volumes per cent, with a range from 52.6 to 59.6. Although the value obtained for whole blood was higher than that of 48.6 volumes per cent found in normal subjects by Dill, Edwards and Consolazio (13), the increase may be due to greater plasma-cell relation in anemic blood. In fact, the average alkaline reserve of plasma is somewhat lower than the normal average of 58 volumes per

TABLE 4. COMPARISON OF OXYGEN PRESSURE IN MIXED VENOUS BLOOD DURING BREATHING ALTERNATELY OF ROOM AIR AND 100 PER CENT OXYGEN

CASE	ROOM AIR				100% OXYGEN			
	Arterial HbO <sub>2</sub>	O <sub>2</sub> arterio- venous difference	Venous saturation, $103 \times \text{HbO}_2$ $\text{Hb} + \text{HbO}_2$	Venous pO <sub>2</sub> at venous pH	Calculated <sup>1</sup> O <sub>2</sub> arterio- venous difference	Venous HbO <sub>2</sub>	Venous saturation, $100 \times \text{HbO}_2$ $\text{Hb} + \text{HbO}_2$	Venous pO <sub>2</sub> at venous pH
	vol. %	vol. %		mm. Hg	vol. %	vol. %		mm. Hg
L. L.	4.7	4.1	11.5	12.4	4.9	1.8	37.5	27.8
F. O. C.	8.0	4.7	41.2	22.0	5.6	4.4	54.6	27.6
S. P.	8.6	3.5	56.4	27.8	4.2	6.9	75.8	38.6
A. M. C.	11.5	3.9	62.5	33.1	4.7	9.5	77.8	40.6

<sup>1</sup> Arterio-venous difference assumed to be increased by 20% (see text).

cent (with a range from 53.5 to 61) found by Dill *et al.* (13) with a similar technic. However, in case A. T., the alkaline reserve of plasma during anemia was 3.4 volumes per cent higher than at recovery, although variation was within normal range.

The arterial pH of the serum was within the normal limits indicated by Robinson (14). On the other part, lack of significant changes in the arterial pH of anemics is a well established fact.

In 4 subjects in whom the arteriovenous difference and the R.Q. were determined, venous pH was calculated by Henderson's nomogram and the Henderson-Hasselbach formula. Henderson's nomogram seemed usable since no change in the electrolyte equilibrium of the anemic patient's blood has been found. In at least two cases pH differences between arterial and venous blood were significantly higher than normal—0.04 and 0.05 instead of 0.02.

*Oxygen Pressure in Mixed Venous Blood.* Changes produced in oxygen pressure of mixed venous blood in 4 anemic patients shifted from room air to 100 per cent oxygen breathing are summarized in table 4. The following data is used in calculations: a) hemoglobin capacity and hemoglobin oxygen content were determined by analysis. The amount of oxygen dissolved in the anemic patient's blood at 37°C. was calculated by the formula of Send-

<sup>3</sup> Volumes per cent of CO<sub>2</sub> taken up by oxygenated blood at CO<sub>2</sub> pressure of 40 mm. Hg and 37°C.

roy, Dillon and Van Slyke (15). We assumed that oxygen represented 94 per cent of the alveolar gas during pure oxygen breathing and that gas diffused normally through lung walls. *b*) Oxygen arteriovenous differences and the cardiac output were measured by the acetylene rebreathing method. During oxygen breathing we did not measure cardiac output and no data are recorded in the literature. Contradictory results on cardiac output in normal subjects breathing oxygen have been reported by Whitehorn *et al.* (16), Harrison *et al.* (17), Grollman (18), Richards and Barach (19) and Otis *et al.* (20). We assumed that changes in cardiac output during anemia showed a relation to drop in pulse rate similar to that observed in Whitehorn's normal subjects. In our anemic patients pulse rate dropped 11 beats per minute during oxygen breathing. Whitehorn's normal subjects, whose pulse rates fell 11 beats, showed a 20 per cent decrease of cardiac output, and this figure was also used to evaluate blood flow changes in anemic patients during oxygen breathing. As we chose the greatest reported value of cardiac output decrease, calculated oxygen pressure of mixed venous blood should be in any event low, a fact which increases reliability of the results.

From table 4 we concluded that in anemia oxygen pressure of mixed venous blood, and therefore in tissues, is lower than normal. When hemoglobin is very low, as in *patient L. L.*, oxygen pressure is about 30 per cent of the normal value. Oxygen breathing increased the oxygen pressure of mixed venous blood in *L. L.* to 80 per cent of normal.

*Heart Rate.* In anemic patients the breathing of 100 per cent oxygen for periods of 15 to 30 minutes reduced the heart rate by an average of 11.2 beats per minute (table 2). On return of hemoglobin to normal, oxygen breathing slowed the heart by 5.2 beats per minute (table 1). This figure falls within values given for normal subjects.

*Cardiac Output.* In 4 anemic patients measurements made by the acetylene method revealed a decrease in arteriovenous differences and a corresponding augmentation of cardiac output, an increase higher at lower hemoglobin levels. These results agree with several studies made either with the rebreathing or direct Fick method.

#### DISCUSSION

Examination of the anemic patients' arterial blood showed oxygen pressures within normal limits, a fact which suggested that there was no hypoxic stimulation of arterial chemoreceptors. Calculation of the tissues  $pO_2$  showed oxygen want despite the increase of cardiac output and greater venous blood acidity; these factors both tend to reduce the fall of the tissues' oxygen pressure.

In summary, anemic patients suffer from oxygen want at the tissue



level. Arterial blood is normal from the respiratory point of view but has a low oxygen content due to hemoglobin loss. These conclusions agree with published data.

During severe anemia average pulmonary ventilation in the resting patients was greater than normal. Proof of such increase was given by the fact that in 3 of the 4 patients followed from severe anemia to recovery ventilation diminished when hemoglobin approached normal levels. Decreased oxygen consumption and little or no change in the oxygen equivalent was observed. The  $\text{CO}_2$  ventilatory equivalent was higher during anemia than on recovery as a result of a low R.Q.

The average oxygen ventilatory equivalent of anemic patients as a group was slightly higher than in a group of normal subjects. In one case the oxygen equivalent was beyond the highest normal limit during anemia but did not change on recovery.

Results obtained by Tomkins, Brittingham and Drinker (4) and Richards and Strauss (5) on patients during anemia and on recovery indicated that ventilation increased during anemia only in cases in which there was a rise of oxygen consumption and carbon dioxide production. In patients with hyperventilation  $\text{O}_2$  and  $\text{CO}_2$  ventilatory equivalents showed little or no change from anemia to recovery.

Parallelism between greater ventilation and  $\text{O}_2$  consumption or  $\text{CO}_2$  production suggests that hyperventilation is mainly due to increased metabolism, which is evidenced by the slight or unapparent change in ventilatory equivalents on recovery. On the other hand, the failure of ventilation to increase in all anemic patients, even though tissue hypoxia is assumed to exist in every case, argues against an hypoxic origin of hyperventilation.

It does not seem justifiable to establish a causal relation between anemic hypoxia and hyperventilation. The latter appears due largely to greater metabolic rate and, perhaps in a lesser degree, to diminished buffer power of the blood. As stated by Barr and Peters (21), the loss of the buffer effect of blood for  $\text{CO}_2$ , due to a low hemoglobin content, produces greater changes of  $\text{CO}_2$  pressure and pH at the tissues level. This variation tends to stimulate the respiratory center and to produce hyperventilation.

If agreed that there was no direct hypoxic stimulation of the respiratory center in anemia, then it is not surprising that oxygen breathing, which increases the tissues'  $\text{pO}_2$ , did not depress pulmonary ventilation. Oxygen breathing actually increased respiratory volume more than normal.

The increase of oxygen pressure at tissues level by oxygen breathing was attributable to about 1.9 volumes per cent more gas dissolved in arterial blood. In cases of severe anemia this volume represents an important proportion of total oxygen content, 37 per cent in one anemic patient.

Oxygen pressure of mixed venous blood is a criterion which only represents the average of oxygen pressures of the different tissues and not the actual  $pO_2$  of the respiratory center. But if the greater slowing of heart rate in anemic patients breathing pure oxygen is due to an increase of the  $pO_2$  of the cardiac centers<sup>4</sup>, logically oxygen pressure at the respiratory center must also increase. Since oxygen breathing hinders  $CO_2$  transport in anemic patients by diminishing reduction of oxyhemoglobin in the tissues, one may argue for a rise of  $pCO_2$  at the respiratory center and for stimulated ventilation. On the other hand, if the rise of ventilation in anemia were caused by curtailed oxygen supply to the respiratory center, respiratory stimulus would tend to decrease during oxygen breathing.

Changes in ventilation should be the algebraic summation of stimulation and depression under oxygen breathing in anemia; stimulation would be greater and would predominate over depression and hyperventilation would result. No evidence supports such an hypothesis. On the other hand, acute carbon monoxide hypoxemia (similar in many respects to anemic hypoxia) did not stimulate the respiratory center in man and dogs (2). This fact supports the idea that oxygen lack from anemia does not excite the respiratory center. Methemoglobin hypoxemia studied in unanesthetized dogs by Clark, Van Loon and Adams (3) leads to an analogous conclusion.

The existence of a direct hypoxic stimulation of the respiratory center has not been proved in resting anemic patients. Evidence favors a very low sensitivity of the center to anemic hypoxemia.

#### SUMMARY

Lung ventilation in air and pure oxygen has been measured in anemic patients. Oxygen pressure at tissue level was calculated. Findings were as follows: 1) Ventilation was increased in most anemic patients. Such increased ventilation seemed to be due chiefly to greater oxygen consumption or carbon dioxide production and perhaps, in some degree, to loss of the buffer power of the blood; 2) oxygen breathing always increased ventilation in anemic patients; 3) as in carbon monoxide and methemoglobin hypoxemia, there was no proof of direct hypoxic stimulation of the respiratory center during anemia.

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## *Resuscitation from Nearly Fatal Effects of Exposure to "Pure" Carbon Monoxide\**

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IN A PREVIOUS REPORT (1) we have published the results obtained in a comparative study of the effectiveness of several commonly used methods of resuscitation in dogs asphyxiated with 0.3 per cent carbon monoxide in the form of diluted illuminating gas. This is a report of a similar study made on dogs asphyxiated with 'pure' cylinder carbon monoxide<sup>1</sup> in concentrations of 0.3 per cent, 2 per cent and 5 per cent.

### METHODS

The experimental conditions of this study were similar to those used in the previous study, with the exception of the source of the carbon monoxide. A total of 182 dogs was used. They were divided into eight groups which received various treatments after asphyxiation. In seven of the groups the dogs were removed from the gassing chamber as soon as possible after the first respiratory gasp. (In a previous report it was shown that this was the most reliable point at which to start resuscitation.) In one group *F* the dogs were not removed until one minute after the last respiratory gasp.

The following procedures were used on the dogs asphyxiated with 0.3 per cent carbon monoxide: *A*, no treatment except removal to uncontaminated air; *B*, manual artificial respiration with inhalation of 7 per cent carbogen<sup>2</sup> *C*, mechanical artificial respiration with a 'suck and blow' type of resuscitator<sup>3</sup> using 100 per cent oxygen; *D*, the same as *C* except for the use of 7 per cent carbogen; *E*, mechanical artificial respiration with a bellows type of positive pressure resuscitator<sup>4</sup> using 7 per cent carbogen; *F*, the same as *D* except that the treatment was begun one minute after the last respiratory gasp.

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<sup>1</sup> Obtained from the Matheson Co., East Rutherford, N. J.

<sup>2</sup> A mixture of 7 per cent carbon dioxide and 93 per cent oxygen.

<sup>3</sup> Either the Emerson or the E & J.

<sup>4</sup> McKesson Resuscitator.

Twenty-five dogs (*groups G and H*) were exposed to 2 per cent and 5 per cent concentration of carbon monoxide respectively, and were treated with 7 per cent carbogen administered by a resuscitator of the 'suck and blow' type.

The dogs used were mongrels of both sexes and varying ages ranging from 3 to 14 kilograms in weight. After resuscitation all surviving animals were kept under observation for at least 14 days unless death occurred earlier.

TABLE 1. SHOWING THE RESULTS OF VARIOUS TYPES OF TREATMENT

GROUP	PROCEDURE AND TREATMENT	CO USED	DOGS USED	NO. DIED	NO. SURV.	SURV.	NEU-ROL. SEQUEL.	NEU-ROL. SEQUEL.	NO. WITH PNEUMONIA
		%				%	%	%	
A	No treatment	0.3	20	17	3	15	2	67	0
B	Manual with 7% carbogen	0.3	30	15	15	50	7	46	1
C	Mechanical <sup>1</sup> with 100% oxygen	0.3	30	16	14	47	12	85	2
D	Mechanical <sup>1</sup> with 7% carbogen	0.3	30	15	15	50	11	73	0
E	Mechanical <sup>2</sup> with 7% carbogen	0.3	30	18	12	40	8	67	1
	Response to treatment		120	64	56	46	38	68	4
F	Mechanical <sup>1</sup> with 7% carbogen applied 1 min. after last respiration	0.3	17	17	0	0	—	—	—
G	Mechanical <sup>1</sup> with 7% carbogen	5.0	10	1 <sup>3</sup>	9	100	0	0	0
H	Mechanical with 7% carbogen	2.0	15	1 <sup>3</sup>	14	100	1 <sup>4</sup>	7	3

<sup>1</sup> The E. & J. or the Emerson apparatus was used

<sup>2</sup> The McKesson apparatus was used.

<sup>3</sup> Showed no air hunger; removed pulseless after 2 minutes of complete apnea.

<sup>4</sup> One died after 4 days after being normal for 1 day ('clear period'); small hemorrhages in white matter of frontal lobes.

The dogs which were unable or unwilling to eat were fed daily with warm whole milk administered by stomach tube in amounts they could tolerate. The dogs which died before the end of the 14-day period, and those which survived that period but developed signs of neurological damage were examined post-mortem for gross pathological changes in the lungs and brain.

The asphyxiation chamber has been described (1). During exposure to the carbon monoxide, observations were made on the behavior of the animals. At the onset of the first respiratory gasp, 'air hunger,' the dogs were

removed from the chamber as soon as possible (in about five seconds) and the treatment was begun. The nature of the pulse and its changes (by palpation of the chest) were noted as well as the character and duration of the respiratory efforts.

Blood samples were drawn at intervals from some of the survivors for the determination of the rate of elimination of carbon monoxide. The results obtained in this part of the study will be included in another report.

## RESULTS

Table 1 presents a summary of our data on the incidence of survival and of post-resuscitation sequelae.

Among the dogs exposed to 0.3 per cent carbon monoxide, 3 survived of the 20 animals which received no treatment except removal from the gassing chamber. The survival ratio among the treated groups ranged from 40 per cent to 50 per cent, the average ratio for the entire group of 120 dogs being 46 per cent. The difference between the 120 treated dogs (*groups B, C, D, and E*) and the untreated *group A* is statistically significant, ( $X^2 = 7$ ). It is evident that treatment, either manual or mechanical, is better than none, and that manual artificial respiration is as effective as mechanical artificial respiration in dogs asphyxiated with "pure" carbon monoxide.

In *group F*, in which one minute was allowed to elapse after the last respiratory gasp before treatment was begun, there were no survivors.

In *groups G and H*, which were asphyxiated with a high concentration of carbon monoxide (5 per cent and 2 per cent, respectively) the survival ratio was 100 per cent in all the dogs which exhibited air hunger. Two dogs, one in each group, showed no air hunger. They were removed with no palpable pulse after approximately two minutes of apnea and could not be resuscitated.

As a consequence of the asphyxiation with 0.3 per cent carbon monoxide, 40 of the 59 survivors developed signs of neurological disturbance, but in 3 dogs the behavior changes were transitory and disappeared within 2 to 10 days. Although as a general rule evidence of neurological change could be observed immediately after resuscitation, in 5 dogs they did not appear until a 'clear period' of 2 to 7 days had elapsed. Only one of the 23 dogs surviving the asphyxiation with high concentrations of carbon monoxide manifested signs of neurological damage which became apparent after 24 hours of normal behavior. This dog died on the fourth day after resuscitation.

There was considerable variation in the type and the degree of nervous system involvement. Three of the dogs remained comatose until death occurred, 2 to 6 days after resuscitation. The other 37 exhibited, in varying degrees of severity, the usual neurological sequelae of weakness, ataxia,

spasticity, listlessness, and anorexia, which we observed in our study of dogs asphyxiated with diluted illuminating gas (1).

The brains of all dogs which manifested permanent neurological sequelae were examined grossly after death. Evidence of damage was found in 17 (42 per cent) of the 40 dogs. The most common findings were cortical vascular congestion, hemorrhage, and edema. Minute petechiae were seen in various parts of the brain stem in several dogs. The brains of the remaining 23 dogs appeared to be normal, but evidence of damage may have

TABLE 2. SHOWING RELATION OF PALPABLE PULSE TO SURVIVAL

GROUP	PROCEDURE AND TREATMENT	NO. DOGS	WITH PULSE ON REMOVAL				WITHOUT PULSE ON REMOVAL			
			No. with	Lived	Died	Lived	No. without	Lived	Died	Lived
A	No treatment	20	8	3	5	37	12	0	12	0
B	Manual with 7% carbogen	30	18	13	5	71	12	2	10	16
C	Mechanical with 100% oxygen	30	19	13	6	68	11	1	10	9
D	Mechanical with 7% carbogen	30	21	15	6	70	9	0	9	0
E	Mechanical with 7% carbogen	30	15	12	3	80	15	0	15	0
F	Mechanical with 7% carbogen applied 1 min. after last respiration	17	3	0	3	0	14	0	14	0
G	Mechanical with 7% carbogen	10	9	9	0	100	1 <sup>1</sup>	0	1	0
H		15	14	14	0	100	1 <sup>1</sup>	0	1	0

<sup>1</sup> Showed no air hunger and removed after two minutes of complete apnea.

Groups A, B, C, D, E and F were asphyxiated with 0.3 per cent CO; group G with 5 per cent CO; group H with 2 per cent CO.

been found if microscopic examination had been made. In general there was no consistent correlation between the degree of change in behavior and the degree of pathological change seen on gross examination post-mortem. For example, one dog which survived for three days in a comatose state had no evidence of gross brain pathology at autopsy, while another which developed a slight listlessness and a tremor had, at death on the fourth day after resuscitation, an extreme congestion of the cortex and meninges.

Lung pathology was discovered post-mortem in 7 of the survivors and 4 of these also had pathological changes in the brain. The lungs in each case were one-quarter to one-half consolidated. It is probable that pneumonia

developed subsequent to asphyxiation in the 6 dogs which died between the seventh and fourteenth day after resuscitation. Since the remaining dog died on the second day with lungs about one-third consolidated it is likely that the pulmonary infection was established before the animal was used in the experiment. It is of interest that death from pneumonia occurred in 3 dogs which were exposed no longer than five minutes to 2 per cent carbon monoxide.

After resuscitation was begun rhythmic respiratory movements of 'normal' character were resumed in approximately three minutes in the dogs surviving asphyxiation with 0.3 per cent carbon monoxide, with the ex-

TABLE 3. SHOWING THE RELATION OF EXPOSURE TIME TO SURVIVAL

TIME OF EXPOSURE <sup>1</sup>	NO. DOGS	NO. DIED	NO. LIVED	SURV.	AVERAGE TIME ELAPSING BETWEEN START OF EXPOSURE AND			
					No. dogs	First symptom	First gasp	Total time exposed
				%				
More than 60.5 min.....	58	24	34	59	64	14.0	77.3	91.3
Less than 60.5 min.....	82	57	25	30	93	11.2	29.1	40.3
TOTAL.....	140 <sup>2</sup>				157			

<sup>1</sup> Average time, 60.5 min.

<sup>2</sup> Does not include group F.

ception of 3 animals which were treated with 100 per cent oxygen (*group C*). These animals required 11, 12, and 14 minutes of mechanical resuscitation before endogenous respiratory movements were strong enough to maintain adequate ventilation.

In the two groups exposed to high concentrations of carbon monoxide (*groups G and H*) respiration was resumed within a mean time of two minutes with a range of 1 to 5 minutes. In several dogs vigorous respiratory gasps continued for 3 to 4 minutes, superimposed upon the normal type of respiratory rhythm.

In table 2 we have summarized the results showing the relation of a palpable pulse at the beginning of treatment to chances of survival. Among the dogs asphyxiated with 0.3 per cent carbon monoxide and removed at the onset of air hunger, the animals which were given either manual or mechanical artificial respiration and had a palpable pulse had a survival ratio of 68 to 80 per cent. On the other hand only 3 of the 47 dogs without a palpable pulse survived. The fact that 2 of these were treated with manual artificial respiration suggests that the thoracic manipulation may have stimulated the heart through a massaging action. The low survival ratio among the dogs receiving no treatment (37 per cent) also indicates the value



of thoracic manipulation as well as the inhalation of oxygen in maintaining cardiac function. The difference in survival between the non-treated and the treated groups among the animals which had a palpable pulse at the onset of air hunger is statistically significant ( $X^2 = 4.3$ ).

Of the 17 dogs in which treatment was begun one minute after the onset of air hunger, only 3 had a pulse which was barely palpable, continued to weaken, and was no longer perceptible after one minute of treatment.

All the dogs exposed to high concentrations of carbon monoxide and removed at the onset of air hunger had a pulse and were resuscitated. The

TABLE 4. RELATION OF EXPOSURE TIME TO NEUROLOGICAL SEQUELAE

TIME OF EXPOSURE	NUMBER OF DOGS			NEUROL. SEQUELAE
	Surv. total	Normal	Neurol. sequelae	
More than 60.5 min.....	34	6	28	% 82
Less than 60.5 min.....	25	13	12	48
TOTAL.....	59	19	40	67

pulse was markedly arrhythmic, slow and almost invariably strong at the beginning of treatment, but became much more regular and faster within 10 minutes after the resumption of respiratory movements.

The relation between the length of exposure to 0.3 per cent carbon monoxide and the chances of survival is shown by the data in table 3. The dogs which were treated at the onset of air hunger are divided into 2 new groups: 1) those exposed more than the mean exposure time of 60.5 minutes and 2) those exposed less than this time. Contrary to expectations, the 58 dogs with the longer than average exposure had a higher survival ratio (59 per cent) than the 82 dogs which were exposed for shorter periods (30 per cent). This marked difference, which is statistically significant ( $X^2 = 8.1$ ), in the ability to survive indicates the existence of a physiological difference between the members of these 2 groups in regard to their reaction to asphyxiation with carbon monoxide.

From the data in table 3 it is seen that the first sign of anoxia appeared at approximately the same mean time in each group, namely, 14 minutes in the groups exposed longer than 60.5 minutes and 11.2 minutes in the other group. In the ensuing period, however, between the first sign of anoxia and the onset of air hunger, the difference is very great; 77.3 minutes as compared to 29.1 minutes.

Concomitant with the longer exposure period in the resistant group of

dogs is the longer period of anoxia, which is reflected in the higher incidence of neurological sequelae in the survivors of this group. The data are summarized in table 4. The difference in the incidence of neurological sequelae between the two groups is statistically significant ( $X^2 = 10.7$ ).

#### DISCUSSION

The conclusions to be drawn from the data presented above in regard to the dogs asphyxiated with 0.3 per cent carbon monoxide are: 1) that artificial respiration, manual, with the inhalation of 7 per cent carbogen, or mechanical, with the inhalation of carbogen or 100 per cent oxygen, effectively increases the number of survivors; 2) that the chances of survival are dependent to a large extent upon the resistance of the cardiovascular system to the toxic action of carbon monoxide asphyxia; 3) that animals which arrive at the stage of air hunger after a prolonged period of exposure to anoxia have a much better chance of being resuscitated than those in which the air hunger stage is attained more rapidly; and 4) that the increase in chances of post-resuscitation neurological sequelae parallels the increase in the time of exposure to the anoxia caused by carbon monoxide.

In regard to the dogs asphyxiated with high concentrations of carbon monoxide, and consequently for only a few minutes, resuscitation by means of a mechanical resuscitator with 100 per cent oxygen is invariably successful largely because cardiovascular function, though somewhat impaired, is quickly restored. It is probable that no treatment except removal from the asphyxiating chamber would have been equally successful. Likewise, the brief asphyxiation is inadequate to produce the large incidence of neurological disturbance which appeared in the dogs exposed for longer periods to 0.3 per cent carbon monoxide.

From the data on the survival of dogs exposed to 0.3 per cent carbon monoxide in this study, the inevitable conclusion would be that artificial respiration induced by means of a mechanical resuscitator has no advantage over manual respiration with the inhalation of 7 per cent carbogen. But in our previous study (1) on a larger number of animals asphyxiated with illuminating gas, we demonstrated that mechanical artificial respiration is unquestionably the more effective method, since we resuscitated 125 of 186 dogs (67 per cent) treated in this way, and only 23 of 50 dogs (46 per cent) treated by manual respiration. Since the experimental conditions were the same except for the source of the carbon monoxide, the different results obtained must be due to some difference in the asphyxiating gas.

As in our previous study (1), we have found that resuscitation depends on the resumption or maintenance of adequate circulation. However, analysis of our data show that there are significant differences in the two

studies as regards the effect of the gas used on the presence of a palpable pulse after asphyxiation, and on the chances of resuscitating the dogs in which a palpable pulse was present. These data are summarized in table 5. It is evident that among the dogs asphyxiated with 'pure' carbon monoxide fewer had a palpable pulse (61 per cent compared to 71 per cent) and that of these fewer could be resuscitated (55 per cent compared to 94 per cent). Likewise in the 'pure' carbon monoxide group a greater proportion had no pulse (39 per cent compared to 29 per cent), and the chances of survival in this group were practically nil (2.9 per cent), while in 19 per cent of the dogs without a palpable pulse in the illuminating gas group the resumption of an

TABLE 5. COMPARISON OF THE RELATION OF THE PULSE TO CHANCES OF SURVIVAL IN DOGS ASPHYXIATED WITH 'PURE' CO AND WITH DILUTED CHICAGO ILLUMINATING GAS

ASPHYXIATING GAS WITH CO OF 0.3% DILUTED WITH AIR	NO. DOGS USED	DOGS WITH PULSE				DOGS WITHOUT PULSE			
		No. Dogs	With pulse	No. dogs surv.	Surv.	No. dogs	Without pulse	No. dogs surv.	Surv.
			%		%		%		%
'Pure' CO.....	90	55	61	30	55	35	39	1	2.9
Chicago illuminating gas....	186	134	71	126	94	52	29	10	19.0

adequate cardiovascular function resulted in resuscitation. These striking differences in the effect on the cardiovascular system point to some difference in the action of the two asphyxiating gases.

Our observations that the dogs exposed for long periods to 0.3 per cent carbon monoxide had a much better chance of immediate survival than those exposed for short periods, when the mean exposure time for all the dogs is used as the dividing line, is not in accord with the results we obtained with dogs exposed to diluted illuminating gas. The latter results showed no difference in chances of survival when the same criterion is applied. The possibility that the concentration of carbon monoxide was not the same in the two groups is very remote, since periodic analyses of the carbon monoxide content of the air in the asphyxiating chamber were made in both cases. Furthermore, we have repeatedly observed that 2 dogs exposed in the chamber at the same time manifest air hunger at widely disparate intervals after gassing was begun; in some cases one dog remained in the chamber three times as long as the other.

The reasons why certain dogs are able to withstand carbon monoxide asphyxia for much longer periods than others are difficult to ascertain with the available data. Three possible explanations can be offered. The resistant dogs may 1) absorb carbon monoxide at a slower rate, 2) oxidize carbon monoxide to carbon dioxide, and 3) make physiological adjustments

which decrease the oxygen demand of the tissues after establishing an equilibrium between the alveolar carbon monoxide and the blood carbon monoxide content, at a level which causes the onset of air hunger in the less adaptable animals. A decrease in the uptake of carbon monoxide would depend on any or all of these changes: *a*) a decreased minute respiratory volume, *b*) a decreased circulation time and *c*) a decreased rate of formation of carboxyhemoglobin. Diminished ventilation occurs only in advanced cases of carbon monoxide asphyxia as a result of terminal depression of the respiratory center (2, 3). Most workers report either no change (4, 5, 6) or an increase (7, 8). A decreased circulation is unlikely in view of the observations of Chiodi *et al.* (6) that the cardiac output and the pulse rate are increased when 30 to 50 per cent of available hemoglobin is changed to carboxyhemoglobin. An increased pulse rate has also been reported by other authors (9, 10). There is no evidence that there is any great difference in the rate of formation of carboxyhemoglobin in the blood among members of the same species. It appears unlikely that a diminished rate of uptake of carbon monoxide can account for the prolonged exposure of the resistant animals.

Although it has been shown that carbon monoxide can be oxidized to carbon dioxide by muscle tissue *in vitro* when high concentrations of carbon monoxide are used (11, 12), this reaction is of no significance under physiological conditions in which much lower concentrations are involved, since Roughton and Root (13), using radioactive CO in man were unable to detect any radioactivity in the exhaled CO<sub>2</sub>.

Since we have made no determinations on the uptake of carbon monoxide, we do not know how much of an interval elapses between the time when the carbon monoxide saturation of the blood reaches the concentration found at air hunger (approximately 74 per cent for 61 dogs, range 60 to 88 per cent) and the time when air hunger appears. It is conceivable that this high concentration is attained in all dogs within approximately the same time, but that air hunger appears at this point only in those dogs in which physiological adjustments to the decreased oxygen supply have not occurred. In those dogs in which adjustments to anoxia have occurred the onset of air hunger is delayed until the oxygen requirements exceed the oxygen supply as the asphyxia becomes more acute. It is likely that the blood saturation with carbon monoxide increases very slowly when the concentration is already high and that in some cases an equilibrium may be established between the alveolar carbon monoxide and the carbon monoxide in the blood, with no further increase in the amount of blood carboxyhemoglobin. Under the latter conditions, if the oxygen demand of the tissues is decreased in carbon monoxide asphyxia as has been reported in

asphyxia caused by inhalation of 6 to 7 per cent oxygen (14), it is conceivable that a dog could live for a considerable period before the prolonged asphyxia would precipitate air hunger. In the absence of adequate data these speculations are offered as the most plausible explanation for the extraordinary resistance of some of our dogs to the immediate effects of carbon monoxide.

The after-effects, in survivors of carbon monoxide asphyxiation, are in the greatest proportion in the animals with the longest exposures. This is the result of prolonged anoxia acting upon the central nervous system. The fact that the incidence of neurological sequelae is higher in dogs exposed to 'pure' carbon monoxide (67 per cent) than in those exposed to diluted illuminating gas (43 per cent) (1) again demonstrates the existence of some difference between carbon monoxide when used alone, and when mixed with other constituents of natural gas. This difference, however, is probably due to the longer average exposure (51 min.) to 'pure' carbon monoxide than to carbon monoxide in illuminating gas (47 min.).

As indicated above we believe that the 'pure' carbon monoxide used in this study was more toxic than the illuminating gas in our previous study on the basis of the percentage of animals resuscitated. With the 'pure' carbon monoxide 46 per cent were resuscitated with mechanical resuscitators and with illuminating gas 67 per cent were resuscitated. In addition our observations on the pulse indicated that the 'pure' carbon monoxide had a greater cardiotoxic action than the illuminating gas on the least resistant group of dogs.

Either a contaminant gas in the former caused the increased toxicity, or the degree of toxicity is the result of the action of carbon monoxide alone which is modified by the presence of other gases in the illuminating gas. The 'pure' carbon monoxide used in these experiments had the following composition: carbon monoxide, 91-93.8 per cent; nitrogen, 4-5 per cent; hydrogen, 2-3 per cent; carbon dioxide and oxygen, 0.2-1 per cent. Since the carbon monoxide was diluted to 0.3 per cent by mixing it with air in the asphyxiating chamber it is obvious that any toxic contaminant which escaped detection would be so dilute that it can be ignored as a source of error. The chief constituents of the illuminating gas we used are methane, 56.5 per cent, hydrogen, 27.1 per cent, and ethane, 6.9 per cent. Since methane was present in a concentration of approximately 5.6 per cent in the asphyxiating chamber, it is suggested as the agent which may exert an inhibiting action on carbon monoxide in vivo. This is a matter which must be determined by experiment.

This difference impresses us as significant because if the toxic action of carbon monoxide were due only to anoxemia resulting from the replacement of oxygen with carbon monoxide in the hemoglobin of the erythrocyte,

there should be no difference between the effects of the gas when mixed with other constituents of illuminating gas, and when used in the 'pure' form. In either case the secondary effect of anoxemia would be anoxia of the heart and central nervous system; both the immediate effects and the sequelae would be of the same type and would appear in approximately the same proportion of the survivors, considering the large number of animals used in these studies. This indicates that carbon monoxide acts on another site other than hemoglobin and one suspects the heme compounds involved in oxidative processes in the tissues. Haldane (15), Schmitt and Beck (16) and di Prisco (17) concluded that there was a direct effect, probably caused by the combination of carbon monoxide with Warburg's ferment. Rix and Ehrhardt (18) reported that the oxygen metabolism of the brain, especially the basal ganglia, is more affected by carbon monoxide than that of the liver and kidney. Nakamura and Takami (19) determined the oxygen metabolism of different sections of brain of rabbits asphyxiated with illuminating gas and with nitrogen until they showed respiratory changes. They found the reduction of oxygen metabolism of the cortex, medulla, Ammon's sector, basal ganglia and cerebellum was greater with carbon monoxide than with nitrogen asphyxia. These observations are significant in the light of the studies of Huszak (20) who found the highest concentration of cytochrome in the central nervous system to be in the cortex and the basal ganglia. No studies have been reported on the inhibiting effect of carbon monoxide on the oxygen metabolism of cardiac muscle in tissue culture.

Thus it seems probable that carbon monoxide has a histotoxic effect. It is suggested that the histotoxic action is the result of the combination of the carbon monoxide with iron-containing enzymes related to hemoglobin, and that the presence of some constituent of natural gas prevents or delays the combination and thus decreases the toxicity of carbon monoxide.

#### SUMMARY

One hundred and fifty-seven dogs were exposed to 0.3 per cent carbon monoxide (commercial cylinder carbon monoxide, diluted with air) until the onset of the first respiratory gasp. Twenty received no treatment except removal from the asphyxiating chamber; 3 of them survived. Thirty were treated with manual artificial respiration with inhalation of 7 per cent carbogen; 15 survived. Thirty were treated with mechanical artificial respiration of the 'suck and blow' type with 100 per cent oxygen; 14 survived. Thirty were treated with mechanical artificial respiration of the 'suck and blow' type with 7 per cent carbogen; 15 survived. Thirty were treated with mechanical artificial respiration of the positive pressure type with 7 per

cent carbogen; 12 survived. Seventeen were treated one minute after the last respiratory gasp, with mechanical artificial respiration of the 'suck and blow' type with 7 per cent carbogen; none survived. Ten were exposed to 5 per cent carbon monoxide and 15 were exposed to 2 per cent carbon monoxide, until the onset of the first respiratory gasp. Except for one dog in each group which did not manifest air hunger, all were resuscitated with mechanical artificial respiration of the 'suck and blow' type with 7 per cent carbogen.

Fifty-nine per cent of the dogs exposed to 0.3 per cent carbon monoxide longer than the mean time of 60.5 minutes survived, and 82 per cent of the survivors suffered neurological sequelae of more than transitory duration.

Thirty per cent of the dogs exposed to 0.3 per cent carbon monoxide less than the mean time of 60.5 minutes survived, and 48 per cent of these suffered neurological sequelae of more than transitory duration.

The possible causes of the difference in percentage of successful resuscitation between the dogs exposed to 'pure' carbon monoxide and to illuminating gas, but otherwise treated alike, are discussed.

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# *Precooling of Blood in the Arteries, Effective Heat Capacity and Evaporative Cooling as Factors Modifying Cooling of the Extremities<sup>1</sup>*

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PREVIOUS PAPERS (1, 2) have given evidence of precooling of arterial blood in transit and have analyzed the thermal exchange of the foot in a steady state. It is proposed here to discuss the effects of such factors on the acute cooling of the hands or feet. In doing so it will be necessary also to consider heat capacity, not only of the tissues but also of the clothing. The effects of clothing have received little attention in physiological literature, since the physiologist is apt to limit his study to the simpler problem of the nude man. Yet in most climates, at least for part of the year, a nude man is no more physiological than he is conventional. The hands and feet have a particular value for studies of clothing, since in this case both the nude and clothed state may be considered physiological over a wide range of environmental temperatures.

The subject under discussion has a practical importance. Both experience and theory demonstrate that the hands and feet are the most difficult areas to protect from cold. The fundamental studies described in the earlier papers arose from investigation of the effects of exposure and this, in turn, from the practical difficulties that had been experienced in the field.

The experiments to be described deal with the local exposure of the hand or foot to temperatures, which were sometimes as low as  $-32^{\circ}\text{C}$ . ( $-25^{\circ}\text{F}$ ). Even though heavy gloves and socks were used, painful cold, or even frost bite, was experienced. Sometimes a vascular reaction of inflammatory type developed, in which marked vasodilatation induced a rapid rise in the surface temperature of a finger. Such reactions have been described by Miller (3) and by Aschoff (4). Attention must be paid to these reactions, since the rapid rise of temperature seems to deny the whole theory of precooling of blood within the arteries. The apparent discrepancy must be resolved.

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## METHODS

The subject sat in an air-conditioned room which was kept at a cool temperature. He was usually lightly clad. One or both hands or a single foot was inserted into a refrigerator box. When necessary, the extremity under examination could be enclosed in a calorimeter. The calorimeter used for the foot was that described by Love (2). When it was used within the refrigerator, the temperature of the ingoing air was reduced to that of the box by passage through a long copper coil. The calorimeter used for the hand was similar but consisted of a large specially made thermos flask. Further details may be found in the official reports (5, 6).

In many experiments the calorimeter was not used. Comparisons of hand, or foot-gear, were made by determining the 'tolerance times' of extremities wearing two different types of protection. Such 'tolerance times' are simple to determine and are a common device of testing laboratories. However, they are liable to give very misleading information, unless complicating factors are taken into consideration.

The temperature within a calorimeter was raised above that of the refrigerator in proportion to the heat given off, and usually fell during the course of an experiment (see legend to fig. 4). The temperatures given in the tables or figures, unless otherwise specified, are the average air temperatures, to which the limb was exposed. The air entered the calorimeter completely dry, so that the humidity was low in all experiments, where a calorimeter was employed. The air movement could only be estimated very roughly; the estimates were some 2 to 3 meters per minute for the foot and possibly twice this value for the hands.

Temperature measurements were made with copper-constantan couples of wire of 0.2 and 0.1 mm diameter respectively. Five were used for the hand (flexor surfaces of the terminal phalanges of thumb, middle and little fingers, and centers of the palm and back of the hand) and four for the foot (dorsal surface of middle phalanx of the middle toe, center of sole, over the Tendo Achilles at the ankle and just below the external malleolus). Average values of the temperatures recorded by the hand thermocouples (if weighted according to the relative areas involved, namely 8.6 per cent, 21.9 per cent, 17.2 per cent, 26.4 per cent and 25.9 per cent respectively, 7) agreed well with estimates made by a long length of wire used as a resistance thermometer (5, 6). An arithmetical mean of the values recorded by the foot thermocouples similarly agreed well with resistance thermometer values (2). In experiments on the feet four additional couples were used to measure the surface temperature of the boots. These were situated over the little toe, center of the sole, and just below both internal and external malleoli.

## EXPERIMENTAL RESULTS

The results obtained will be exemplified by a few abbreviated protocols and figures.

*Experiment 1.* March 14, 1944. *Subject B.* Room temperature 18°C. The two hands were inserted together into the refrigerator at -25°C. with results as indicated

in figure 1. In this experiment only 3 thermocouples were used on each hand. The right hand wore a Canadian aviator's heavy knitted woolen glove, protected by an outer leather shell with curved fingers. This gave as good protection as any standard glove used. The left hand wore a single knitted glove reinforced by a thin rubber glove on either side of it. Rapid cooling occurred in both hands but more rapidly on the right, and precipitous falls in temperature were associated with intense pain. These bouts of pain were followed by return of comfort associated with rapidly rising temperatures. On the left side the temperature of the little finger rose  $18^{\circ}\text{C}$ . from a value of  $-2^{\circ}$  to  $16^{\circ}$  in some 17 minutes. Smaller but equally abrupt rises occurred in the right hand. The very low temperature level recorded from the left little finger was confirmed by the freezing of the inner rubber glove to the skin at this time with later evidence of slight frost bite. All three periods of pain on the right and the single period on the left were almost unendurable, and it was somewhat a matter of chance that the 'tolerance time' was recorded as 92 minutes for right hand and greater than this for the left.

These increases in temperature induced by vasodilatation were the largest observed in this series of experiments. Similar but smaller increases were seen in *experiment 2* on another subject particularly on the right hand, but were entirely undetectable in either hand in *experiment 3* carried out at a day's interval on the same subject at the same refrigerator temperature but under different environmental conditions.

*Experiments 2 and 3.* Sept. 26 and 27, 1944. *Subject M*, with both hands exposed in the refrigerator at  $-16^{\circ}\text{C}$ . The right hand wore a similar glove combination to that of the right hand in *experiment 1*, except that a light nylon lining and a wool wristlet were added. The left hand wore only 4 light nylon linings under the leather shell and a similar wrist protection. In both experiments the subject sat for one hour in the cool room before inserting the hands into the refrigerator. In *experiment 2* the room was at  $20^{\circ}\text{C}$ . and the subject was warmly clad and comfortable (overcoat and ordinary clothing); in *experiment 3* the room was at  $19^{\circ}\text{C}$ . and the subject wore very little (stripped to the waist, trousers rolled up, arms, lower legs and feet bare). He was very cold before the hands were inserted in the refrigerator. In *experiment 2* the left hand became unbearably painful after 39 minutes, and the right only after 61 minutes. In *experiment 3* both hands became unbearably painful after 21 minutes and no difference between the two hands was detectable. The changes in temperature recorded in the two experiments are shown in figures 2 and 3. In figure 2 the rewarming of the left gloved hand in the air should be noted. On removal of the hand from the calorimeter, the temperatures of the fingers rose rapidly to reach  $20^{\circ}\text{C}$ . within a few minutes. Immediately thereafter the temperature of the palm, which had remained steady, fell abruptly through  $8^{\circ}\text{C}$ . in the next four minutes, until it also reached  $20^{\circ}\text{C}$ . After this the whole hand remained at the temperature level for sometime, a level which happened to be that of the room.

A number of experiments were made on the bare and booted foot of one subject (*M*), and in some of these the boot and sock were worn wet. These experiments were carried out to test the effects of wet cold but serve admirably to illustrate also those of increased heat capacity, since the water is very effective in this regard. Average values for a number of different types

of experiment are given in table 2, and the time relations of the changes in temperature and of the heat loss as measured in the calorimeter in some of these experiments are indicated in figure 4.

The long exposure of *experiment 5* indicates that both surface temperatures and amount of heat loss decrease according to curves which may be approximately represented by exponential equations. By graphic analysis cooling constants may be estimated (see table 2) and also the apparent equilibrium points at which steady states would be attained. In *experiment*

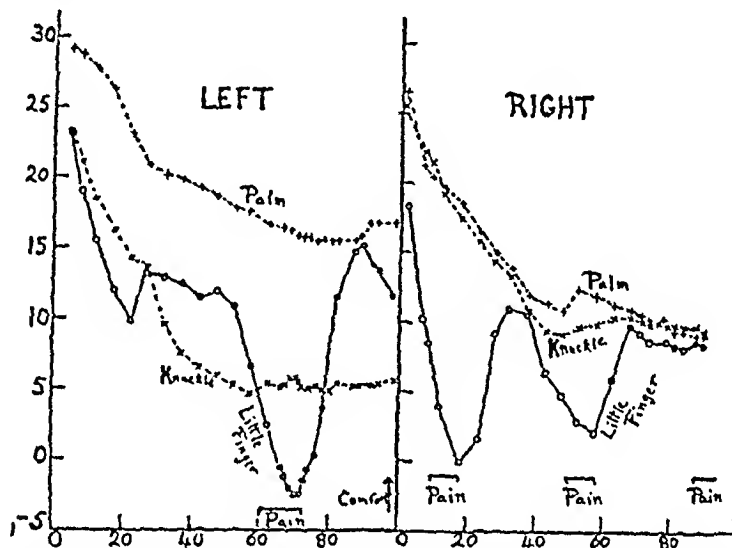


Fig. 1. SURFACE TEMPERATURES of hands in *experiment 1*. Times of exposure, in minutes, are plotted as abscissae and temperatures in  $^{\circ}\text{C}$ . as ordinates.

5 the apparent equilibrium was at a surface temperature of  $5^{\circ}\text{C}$ . and a non-evaporative heat loss of  $21 \text{ Cal/M}^2/\text{hr}$ . The proportion of heat lost by evaporation could increase as cooling progressed, mainly from reduction in non-evaporative loss. The evaporative loss could also show an absolute increase, as in *experiment 5*. However, conditions were complex, owing to possible absorption of water by the clothing at early stages, and the various factors have not been analyzed fully.

#### DISCUSSION

*Vaso-dilation in Reaction to Cold.* Examples of the presence or absence of such responses are seen in *experiments 1* to 3. While there is undoubtedly some individual variation in the degree of reaction, evidence was accumulated that such reactions are absent in any individual, when the cooling is general rather than local, as was the case in *experiment 3*. Only when the subject feels relatively warm, except for local exposure to cold, as was the case in *experiments 1* and 2, is the phenomenon apt to appear. Such relationships favor the hypothesis that the rapid warming of an extremity cannot

occur, when exposure of the arms or legs to cold has induced marked pre-cooling in the arteries within the proximal areas of the limbs. However, when the reactions do occur, the magnitude of the increases in temperature may be surprising. In Aschoff's experiments (4) hands were immersed in ice-water at  $0.3^{\circ}\text{C}$ . The cooling was very local and responses of this type were the rule. They were not obtained in water at a temperature exceeding  $8^{\circ}$  to  $10^{\circ}\text{C}$ . They tended to recur at 30 minute intervals as was the case in *experiment 1*. They were associated with an increased heat output, which

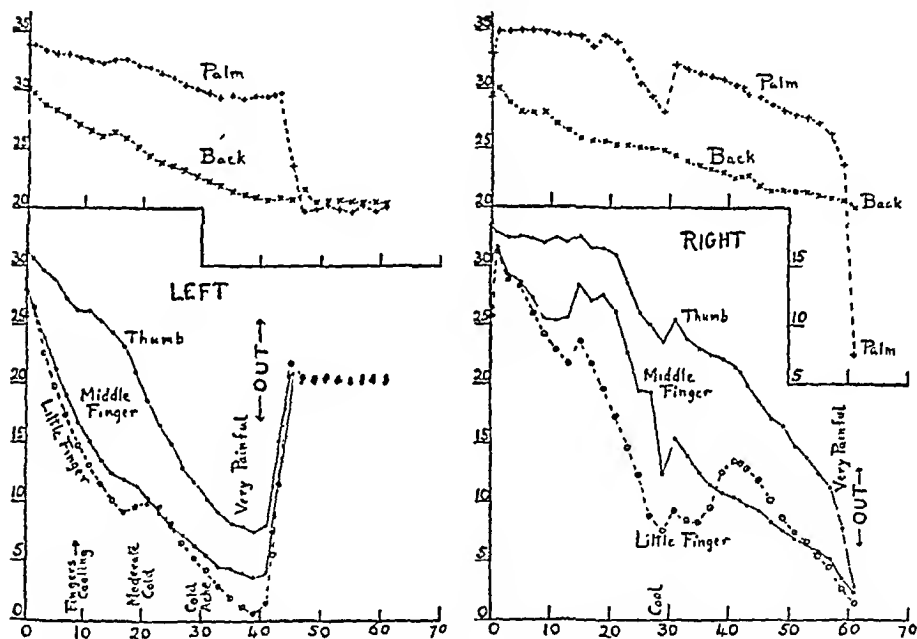


Fig. 2. TEMPERATURES RECORDED in *experiment 2* plotted as in fig. 1. Data on the palm and back of the hand are plotted in an insert above.

might double the total output of the whole hand, though the vasodilation was usually limited to the fingers. Spealman (8) reported increases in blood flow under similar conditions.

The dilatation appears to be inflammatory in type and to be preceded by pain. Arterio-venous anastomoses are likely to be involved (9). The reaction probably depends on an axon reflex, since a similar reaction is described in the cat after section of the posterior roots, provided that the spinal ganglia are intact (10). The initial pain seems to be preceded and possibly to be induced, by a sudden fall of temperature such as might result from an intense vasoconstriction. The development of pain at surface temperature levels of  $8^{\circ}$  or less appears prominently in the description of

Aschoff, the laboratory of the Office of the Quartermaster General, and ourselves, though the pain need not be unbearable if the cooling is not too rapid. The pain is dull but nauseating in type, and shows a considerable degree of spatial summation. Pain limited to one finger is bearable, but if originating from a large area is not. Possibly the pain is determined by acute vasoconstriction and the development of a certain temperature level in the vessels. In this case the more marked symptoms that accompany rapid cooling may depend on spatial summation, since under these conditions the same phenomenon would develop at the same time over a wide area. However, multiple reactions are commonly out of phase, so that local conditions are likely to be mainly responsible for their genesis.

The reactions observed are not incompatible with the existence of pre-cooling of blood in the arterial inflow, since the temperatures reached are not high enough to exclude it. On the other hand if, in such reactions, the return blood flowed back by superficial rather than deep veins, the rapid rise in temperature would be explained more readily. No evidence of such modification of the return path has been advanced.

*Precooling of Arterial Blood and Its Effect of Rewarming.* The rewarming of the left hand after removal from an ice box at  $-16^{\circ}\text{C}$ . to a room at  $+20^{\circ}$ , shown in figure 2, is of particular interest. The abrupt fall in temperature of the palmar surface following the sudden rise in that of the fingers is entirely analogous to the cooling of the brachial artery that develops soon after a cooled hand is rewarmed (1). In point of fact the second experiment reported here was the stimulus that led ultimately to experiments on brachial arterial temperature. It would appear that vasodilatation in the digital vessels returned cooled blood to the neighborhood of the palmar arch, cooling this vessel and inducing a cold arterial inflow into the palmar skin. The whole hand with the high thermal conductivity accompanying vasodilatation attained almost a uniform temperature. It was probably merely a happy accident that this temperature was identical with that of the air and therefore was sustained.

Further evidence of a similar type, though less obvious, is provided by a paradoxical rise in palmar surface temperature that may be seen when the hand is suddenly exposed to a lower temperature. Another instance is a temporary rise in palmar temperature that may result from occlusion of the arterial flow in the arm, when the hand is exposed to cold conditions. Both are explicable on a reduction of the return of cooled venous blood to the palmar arch and it would be difficult to find any other more plausible explanation. One may therefore assume that many bizarre or paradoxical effects probably depend on this heat exchange between vessels. The high skin temperature that is found superficial to an active muscle also may have such

an origin. The vascular supply to the skin penetrates the muscle, so that the arteries might be warmed by venae comites returning heated blood from active muscles.

*Heat Capacity Effects.* A curve of cooling, such as the example given in experiment 5 (fig. 4) may be explained on the basis of an apparent steady inflow of heat and a gradual loss of heat from the cooling tissues. The latter can be represented by an exponential curve. Such an hypothesis was ad-

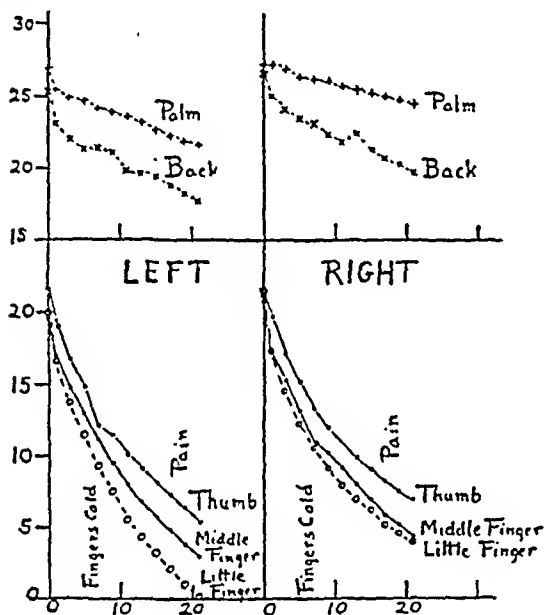


Fig. 3. TEMPERATURES OF experiment 3 plotted as before.

vanced by Hatch (11). In faster cooling, complicated by competitive vasomotor reactions and phasic changes such as those of experiment 1, any such analysis is impossible. However with fast cooling of the whole body, and a consequent absence of such responses, this method of analysis can again be used. It has been applied to the abrupt cooling curves for both hands of experiment 3. Graphs so obtained are shown in figure 5; in this figure the continuous lines represent this experiment, the open circles and ringed crosses representing the right hand and the solid circles and simple crosses the left. The lines are those given by equations of the type

$$\theta - \theta_e = (\theta_0 - \theta_e) e^{-kt}$$

where  $\theta_0$  is the initial temperature,  $\theta_e$  that obtaining in the steady state, and  $\theta$  that observed at any time  $t$ , while  $k$  is a constant which is greater the more rapid the approach to an equilibrium. The values for  $\theta_e$  and for  $k$  estimated empirically from the data are given in table 1. In figure 5 dotted lines are also shown which represent similar cooling curves deduced from the observa-

tions on the left hand in *experiment 2*. It will be noted that, in spite of interruption through the occurrence of mild vasodilator reactions, similar cooling curves were obtained.

Comparison of the values for the left hand in table 1 show that the apparent values of  $\theta_c$  were lower in *experiment 3* than in *experiment 2* (particularly for the whole hand), and that the average values of  $k$  were practically

TABLE 1. APPARENT  $\theta_c$  AND COOLING CONSTANTS  $k$  IN EXPERIMENTS 2 AND 3

	EXP. 2		EXP. 3	
Left Hand	$\theta_c$	$k$	$\theta_c$	$k$
Thumb.....	+2	3.95	-1	3.4
Middle finger.....	-2	3.0	-2	3.0
Little finger.....	-6	3.1	-7	3.7
	<hr/>	<hr/>	<hr/>	<hr/>
Weighted average of hand.....	+10.8	2.97	+5.5	2.75
	<hr/>	<hr/>	<hr/>	<hr/>
Average of all.....	+1.2	3.25	-1.1	3.21
Right Hand				
Thumb.....			+3	4.25
Middle finger.....			-2	3.9
Little finger.....			0	4.25
			<hr/>	<hr/>
Weighted average of hand.....			+11.0	3.85
			<hr/>	<hr/>
Average of all.....			+3.0	4.06

identical. Such values indicate that the rate of cooling on the two days was the same, but that in *experiment 2* the heat input was greater, presumably as the result of a better protection of the inflowing blood in the arm or of a faster rate of inflow. The longer tolerance time in *experiment 2* is therefore explicable on 1) the greater heat inflow; 2) the higher initial temperatures at the time of exposure to the cold; 3) periods of vasodilation postponing cooling. The final 'tolerance' temperatures were very similar in the two experiments.

The comparison of the two types of glove combination is more complex. On simple tolerance times the right combination is 56 per cent more effective than the left on the basis of *experiment 2*, and exactly equal to it according to *experiment 3*. Assuming that the heat inputs in the two hands were equal in *experiment 3*, the values of  $\theta_c$  for the two gloves relative to the environment indicate the corresponding values of the insulations. Utilizing the average values of the table the ratio of the insulations  $R_t/L_t = 1.27$  (since the environment was  $-16^\circ$ ). On this basis the insulation of the right exceeds that of the left by some 27 per cent. None the less on the basis of the rate of cooling the right appears to cool faster than the left by 26 per cent.

The rate of cooling varies inversely as the insulation and inversely also as the effective heat capacity. On the basis of insulation the right hand should cool the slower, and at first glance one would not expect any great difference in the effective heat capacities. However, such an assumption is unwarranted. According to calculations made by G. N. Stewart (12), the heat capacity of each hand should have been about  $0.36 \text{ Cal/}^\circ\text{C}$ . The heat capacity of nylon far exceeds that of wool, so that considering the relative weights and specific heats of the components of the glove combination, (5, 6) the heat capacity of the left combination should have been  $0.064 \text{ Cal/}^\circ\text{C}$ . and that of the right  $0.037$ . The total capacity of the left hand and its

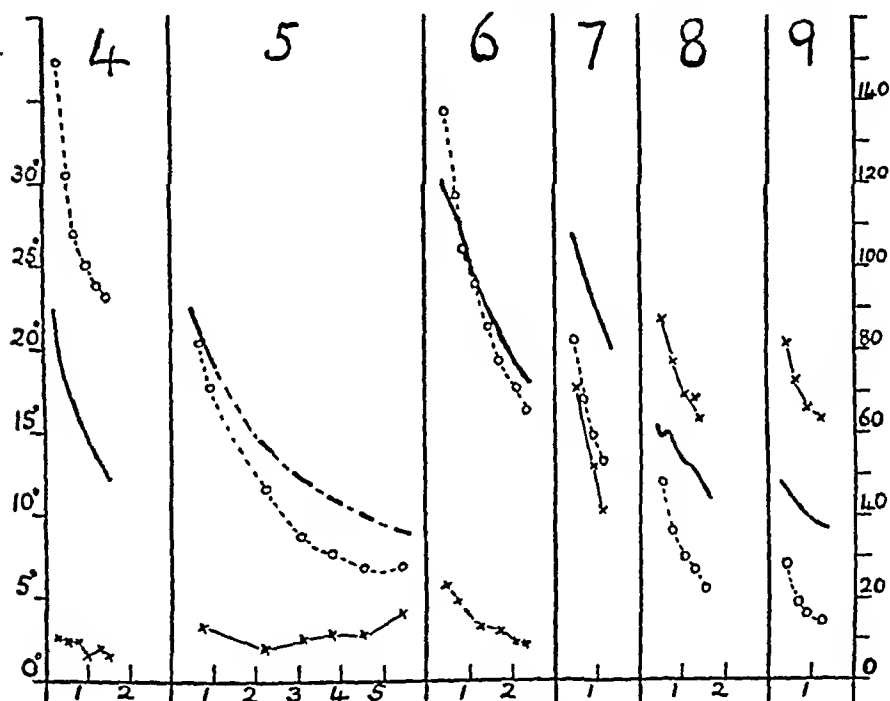


Fig. 4. DATA OF experiments 4 to 9: abscissae indicate time of exposure in hours and ordinates average temperature of the surface of the foot in  $^\circ\text{C}$ . (continuous lines), non-evaporative heat loss (crosses and continuous lines). The scale for temperature is indicated on the left, and that for heat loss on the right. The experimental conditions were as follows: *exp. 4*, bare foot at  $5.75^\circ$  to  $4.85^\circ$ ; *exp. 5*, foot in heavy sock and leather boot at  $4.85^\circ$  to  $2.85^\circ$ ; *exp. 6*, foot in heavy sock, rubber sock and leather boot at  $7.55^\circ$  to  $5.05^\circ$ ; *exp. 7*, foot in heavy sock, rubber sock and wet leather boot at  $4.2^\circ$  to  $3.7^\circ$ ; *exp. 8*, foot in wet sock, rubber sock and wet leather boot at  $4.95^\circ$  to  $3.9^\circ$ ; *exp. 9*, foot in wet sock and wet leather boot at  $2.9^\circ$  to  $2.6^\circ$ . 'Wet' refers to complete soaking in water with drainage of surplus and slight wringing of socks.

coverings should have been  $0.424$  and of the right  $0.397$ , a difference of 7 per cent. However the difference in effective heat capacity must have been very much greater for the capacity of the left glove exceeds that of the right



by 73 per cent, and it is the gloves (with their external position) that undergo the greatest temperature change. On the basis of the probable insulation values of the gloves, one may anticipate a surface temperature of the gloves at the end of *experiment 3* of about  $-5^{\circ}\text{C}$ . or lower. They would have cooled through  $25^{\circ}$  on the outside, and on the inside some  $15^{\circ}$  for the left hand and  $9^{\circ}$  for the right. The change in heat content might be of the order of 1.3 Cal. for the left and 0.6 Cal. for the right. Such differences might be adequate to account for the observed facts.

Actually the changes in heat content in the two limbs would be somewhat greater than that estimated by Stewart, for cooling would not be limited to the area exposed to cold to the extent that he supposed. The spread of heat (or cold) along vessels implies that effects are not limited to one locality, and that heat derived from the forearm may contribute to the heat loss from the hand. Thus it was shown by Bazett and McGlone (3) that immersion of a forearm and hand only in water at  $15^{\circ}\text{C}$ . lowered the temperature in the upper arm (junction of middle and lower thirds) at a depth of 12 mm and close to the brachial vessels from  $36.0^{\circ}$  to  $33.5^{\circ}$  within 15 minutes. Exposure for 52 minutes in another experiment lowered this temperature from  $35.8^{\circ}$  to  $31.3^{\circ}$ . In experiments 2 and 3 the local cooling therefore is unlikely to have been limited to the hand and the estimates for the heat content changes in the tissues are probably too low.

In *experiment 3* the exposure time was very short as the result of the low heat input and the initial subnormal temperatures. The increased heat capacity of the left side was able to balance the effect of poor insulation and so to obliterate differences in reaction. The heat capacity was large relative to the total heat exchange of a short period. In *experiment 2* where the initial temperatures were higher and the heat input greater, the duration of exposure was long enough to make the increased heat capacity of little importance. The greater protection of the right hand resulted in more competition between opposing vascular reflexes and a greater degree of vasodilator reactions. In consequence the protective advantages of the right gloves were exaggerated.

The deceptive temporary protection provided by high heat capacity is exemplified well by the reactions in wet foot gear as opposed to dry, a matter which is again one of practical importance. In table 2 the average heat output is given in  $\text{Cal}/\text{m}^2/\text{hour}$ , and the proportion of this heat loss which was dependent on evaporation is also given. Since there is little point in distinguishing the mode of heat loss, rather than its quantity, in the consideration of wet boots, the total resistance to heat flow is given in terms of 'equivalent Clo units.' This unit is used to represent a comparable dry insulation (14) which, at the observed thermal gradient, would allow an equal (but non-evaporative) heat loss. The equivalent insulation value of the air has been calculated on the same basis, and the difference between

this and the total represents the equivalent insulation value of the boot. All of these 'insulations' have been calculated relative to the surface of the foot. The apparent insulation value of the air for a booted foot is therefore less than that for the bare foot, for the surface losing heat to the air is much the larger. In the last column the rate of cooling of the surface of the foot has been estimated from the data on the assumption that it follows an exponential equation.

The table indicates that a boot and sock together provide insulation more than doubling that given by dry air to the bare foot. The rate of cooling is less than half that of the bare foot. On the other hand a wet boot

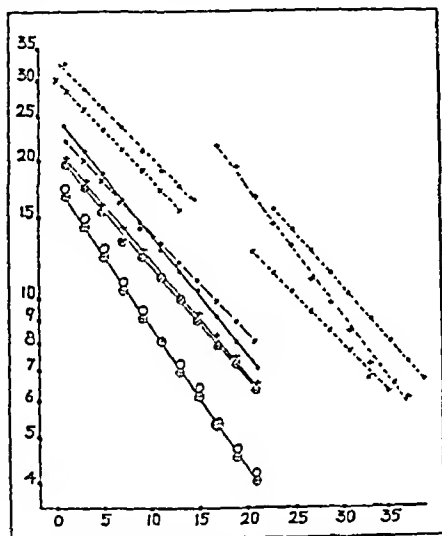


Fig. 5. DATA OF experiment 3. Time is plotted in minutes as abscissae and the degree the temperature exceeded the estimated equilibrium point as ordinates on a logarithmic scale. Data obtained on the thumbs are indicated by vertical crosses, on the middle finger by oblique crosses and on the little fingers by circles. Data from the right hand are indicated by ringed crosses and open circles. Data obtained from the left hand in experiment 2 are shown for comparison and are joined by dotted lines.

and wet sock (*exp. 9*) provide insulation only equivalent to that of the bare foot, yet the rate of cooling is but little faster than that with the dry combination. The heat capacity of the water has masked the loss of insulation. With a short exposure to cold the disability incurred with a wet boot would not be evident. The combination of a wet boot and a wet sock separated by a rubber sock (*exp. 8*) is no better. Evaporative loss from the boot to air occurs as before, and the wet sock gives little insulation. Only the benefit of the high heat capacity, slowing the rate of cooling, is obtainable. On the other hand when the sock below the rubber is dry (*exp. 7*) wetness of the outer boot is of little moment, since it merely reduces the equivalent insulating capacity of the outer boot and air. The combination should be but little inferior to the same sock arrangement combined with a dry boot tested earlier. The fact that no difference was observed probably depended on a chance error from too tight a boot in the dry experiment.

The errors due to heat capacity, if the rate of cooling were to be used to estimate insulation, have been emphasized, since the rate of cooling is the factor that determines 'tolerance times.' 'Tolerance times' would be equally liable to give errors in any rapid test of wet foot gear. Only if mild conditions were used, so that the tests were prolonged, would capacity effects become negligible. Where heat capacity plays a part, it is possible for two combinations tested by 'tolerance times' to appear equivalent at one temperature, while one is the better in rapid tests under severe conditions and the other in long tests with exposure to moderate conditions.

*Evaporative Heat Loss.* The evaporative heat loss forms a large proportion of the total at high temperatures and also at surface temperatures

TABLE 2. EFFECT OF WETNESS ON THE OVERALL EQUIVALENT INSULATION OF BOOTS AND SOCKS

CONDITION	NO. OF EXPS.	TOTAL HEAT LOSS	HEAT LOSS BY VAPORI- ZATION	EQUIVALENT OVERALL INSULATION	EQUIV. AIR INSUL.	COOLING °C/MIN/°C. TEMP. DIFF.
		<i>Cal/m<sup>2</sup>/hr.</i>	<i>%</i>	<i>Clo.</i>	<i>Clo.</i>	
Bare foot	3 incl. exp. 4	83.9	7	0.52	0.52	0.0104
Dry boot & sock	2 incl. exp. 5	47.3	20	1.10	0.36	0.0048
Dry boot & sock with rubber sock	1 (exp. 6)	73.8	12	1.01	0.38	0.0063
Wet boot, dry sock & rubber sock	1 (exp. 7)	94.6	44	1.01	0.25	0.0066
Wet boot, wet sock & rubber sock	1 (exp. 8)	85.8	74	0.48	0.08	0.0068
Wet boot & wet sock	1 (exp. 9)	76.5	82	0.49	0.06	0.0054

20°. It is relatively low at intermediate temperature, as has been shown by Forster *et al.* (15). Insensible perspiration, though low in absolute quantity, may represent a large proportion of the total heat loss in moderately cold conditions, but this is no longer true at extremely low temperatures such as -30°C. At such temperatures cooling of the surface is unable to reduce appreciably the gradient between the surface and the environment, so that non-evaporative loss cannot be reduced significantly by vasoconstriction. Changes in insensible loss from clothed parts are complicated, since fabrics take up or give off water according to the relative humidity. Under cold conditions relative humidity may be raised, even though the absolute humidity is very low, and the water content of the fabrics may change. The actual loss is difficult to predict.

At all low temperatures evaporative heat loss is a liability; it would be useful to be able to prevent it. The evaporative heat loss from wet foot-gear is convenient for studying the possibilities of such control. One might assume that the addition of a rubber sock beneath the boot, as in *experi-*

ments 6, 7, and 8, would remove completely evaporative heat loss from the foot, whether the moisture was derived from insensible perspiration or from wet foot-gear. This is not the case, for it may have little effect. In *experiment 6*, there is no obvious effect on the insensible loss from the combination, nor any improvement in insulation. An apparent loss in insulation was probably due to tightness compressing air spaces. Here evaporative loss was derived from the leather. Evaporation on the skin surface could still go on and the vapor could condense on the inner side of the rubber sock. Heat transfer by evaporation and condensation could occur. Ultimately the sock would have become permeated with water and its insulation value would have been lowered. Such relationships have been demonstrated by the laboratory of the Office of the Quartermaster General.

When the boot outside the rubber sock was wet, evaporative loss could continue from the boot to a much greater extent (*exp. 7*, fig. 5), and the equivalent insulation in the air was lowered. The insulation value of the sock was maintained (until it became saturated with moisture from the skin), so that there was little immediate loss in total insulations. If the sock was also wet, as in *experiment 8*, the equivalent insulation value of both the clothing and air were reduced, and protection was very poor. The presence of the rubber barrier had no appreciable beneficial effect, as may be seen by comparing *experiments 8* and *9*, except in so far that, as the boot dried, ultimately both the insulation of the boot and the normal equivalent insulation of the air could be regained.

Protection from evaporative loss is obtainable if two layers of rubber are worn, one close to the skin, and the other close to the outer insulation. In such an arrangement the sock is prevented from becoming moist either by absorbing perspiration or acquiring water from without. Thus its insulation value is retained. Nor can heat transfer occur from evaporation and condensation across such a double barrier. If a thin cotton sock is worn beneath the inner rubber sock, comfort is improved. Such protection can be worn continuously for at least 1 or 2 days and is particularly valuable in wet cold (16). No tests are shown here of this combination, for the shape of the American service boot did not allow the wearing of this number of layers. The principle is illustrated in the gloves used on the left hand in *experiment 1*. This combination was superior to the standard gloves, but the gain for the hand was only a theoretical one and not of practical value. Such a glove combination was too bulky to allow any fine manipulations, and in practice it had to be removed occasionally to allow use of the hand. On the removal of the glove in a cold environment the moisture, collected beneath the inner rubber, froze and the consequent inconvenience rendered the value of the glove negligible.

## SUMMARY

1. Experiments dealing with the cooling of hands and feet are described to exemplify the rôle of arterial precooling and heat capacity effects in such processes.

2. Rapid increases in surface temperature may occur in the extremities in response to painful cold. However, the temperature levels reached are not high enough to necessitate any modification of the arterial precooling hypothesis. Both during cooling and rewarming after exposure to cold, precooling of arterial blood may produce paradoxical changes in surface temperature. Thus arterial occlusion may cause a temporary rise in the surface temperature of the palm, and vasodilatation during rewarming a precipitous fall of palmar temperature.

3. Heat capacity is an important factor in the rate of cooling of an extremity. The effects produced by relatively small differences in heat capacity of gloves or boots may be great, if the cooling rate be rapid. Measurement of the duration of tolerance to cold can give false impressions as to the value of insulation, unless both vaso-motor reactions and heat capacity effects are given consideration.

4. Owing to the great reduction of convective heat loss in the cold, as the result of arterial precooling, evaporative heat loss may constitute a large proportion of the total loss, particularly at environmental temperatures nearing the freezing level. Possible protection from such loss is described.

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## *Clinical Effects of Noise and Mechanical Vibrations of a Turbo-jet Engine on Man<sup>1</sup>*

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delphia, Pennsylvania*

EXPERIMENTAL DATA are meager as to the physiologic effects of vibrations transmitted to the human body either through solid media, or through the medium of air (1-4), and it is generally conceded that there is no clear-cut evidence nor explanation for normal or pathologic reactions to vibrations (5-8). Therefore, a review of the literature does not *per se* provide adequate basis for suppressing fears and rumors regarding immediate and delayed ill effects upon man supposed to be possible from proximity to jet airplane engines operating at high speed. Increasing use of jet engines necessitates immediate, factual reply to the vague misgivings relating to exposure of personnel in and near these aircraft. It was on this account that experiments using a well-understood turbo-jet engine were undertaken.

### *Effects of Mechanical Vibrations on Man and Lower Organisms*

As early as 1906, it was necessary that formal recognition be given to potentially harmful effects of vibration, as evidenced by the following statement of the British Departmental Committee on Compensation for Industrial Diseases (9):

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<sup>1</sup> The opinions expressed in this article are those of the authors and are not to be considered as reflecting those of the Navy Department.

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Our attention was called to neuroses due to vibration caused by the use of pneumatic tools. Tremor and sleeplessness have occasionally been observed in individuals, but no evidence was obtained of the existence of any nervous disease from this cause which incapacitates from employment.

Numerous studies were conducted from 1918 onward regarding the pathological changes developing in the hands of workers using pneumatic pressure tools and other vibrating implements (10-17). At present, most investigators agree generally as to the symptoms of 'riveter's palsy' which consist of intermittent pain, paresthesias, and a 'feeling of stiffness' of the fingers and hand. These complaints, developing within 2 to 42 months after first using such tools, occur with and are exacerbated by cold (6). A reduced rate of return to normal temperature after exposure of affected hands to cold has recently been demonstrated (17). No organic changes in the blood vessels are noted by biopsy (16) or roentgenography (12), although x-ray interpretation of digital arterial occlusion is presented by at least one laboratory (15). Disagreement still exists, however, as to the exact cause of the syndrome of 'dead hand'.

A variety of other forms of vibrating mechanisms have been designated as the etiologic agents of many disorders in man. In table 1 these devices and their corresponding effects upon man are listed as described by each given author. Similar data for effects on lower animals are summarized in table 2.

Many motivations have prompted the investigations reported in the literature, ranging from the aim to explore unknown realms for fundamental knowledge by the physiologist (4) and the psychologist (31, 32), through the pragmatic applications of the audiologist (33), the automobile engineers' (34, 35) and the aircraft engineers' (5) seeking increased passenger riding comfort, to presumed physiotherapeutic uses (23) and even to uncritical, curiosity-inspired meanderings in these new fields (36, 37). The latter type of reports lend themselves, unfortunately, to indiscreet dissemination, and often, surprisingly enough, by ordinarily circumspect sources (38-40).

The mechanisms of vibratory sense perception are not unequivocally determined. Geldard (31) traces the historical aspects of the theories of separate modalities for vibratory and tactual perception and provides experimental evidence of his own to support his conclusion of a unitarian receptor, namely, the pressure sense. Bekesy (41), on the other hand, reporting experimental stimulation of small areas of skin concludes that sensations of vibration and pressure are separately localized:

The sensation of vibration arises from stimulation of nerve endings in the hair papilla and the sensation of pressure arises from stimulation of nerve endings near the sebaceous gland and, on the surface of the skin, about 0.5 mm. distant from the point sensitive to pressure.

Whether the 'pallesthetic organs' subserve one or more sensibilities remains to be seen. Périllou and Pieron (42) emphasized the view that it is the acceleration imparted to the skin and not the pressure imposed upon it that stimulates vibratory reception. It has been shown by Ahrens (43) that the upper extremities are more sensitive to vibration than the lower extremities. Keighley (44) confirmed Weitz' (45) finding that cold raises the threshold for vibration of human skin, as well as Newman and Corbin's (46) report that vibratory threshold increases with advancing age. Experiments on acute injury to large nerves led Denny-Brown and Brenner (47) to advance the theory that damage to a nerve's sheath of Schwann releases irritating substances into the surrounding tissues. According to de Takats' (18) extrapolation of this theory, chronic traumatic vibration,

e.g., suffered by the hands of pneumatic drill operators, could cause the neural injury described by Denny-Brown and Brenner (47) and thus account for the clinical symptoms. Finally, it is to be recognized that great variation exists in individual sensitivity to vibration (5, 48-51); Kulikovsky (8) has even classified the individual susceptibilities to vibration into three progressively graded groups.

Whereas no definite frequency limits of vibratory perception by man are as yet recognized, figures issued by a number of laboratories concur in fixing the lower limit at about 15 cps and the upper limit at about 1500 cps (5, 7, 33). No unit of vibratory intensity has been accepted universally as a standard: the decibel (52-54) is often used as a physical unit of vibration, the neper (54-56) as a unit of damping of vibration. As units for level of sensation of vibration the 'pal' (57) and 'trem' (5) have been suggested. McFarland (5) points out in a graph based on Reiher and Meister's (1) data that the minimum threshold for response to vibration (measured in 'trem's') is of the same order of magnitude as the minimum threshold for sound (measured in 'phons', 54); for the higher accelerations both sound and vibratory stimuli become 'troublesome' at the same order of magnitude. Schubert (7) cites references upon vibratory discomfort in vehicles which provide figures asserting that frequencies of 7 cps at an amplitude of 0.002 cm. and of 2 cps at 0.005 cm. can just be noted, while amplitudes of 0.004 and 0.013 cm., respectively, cause these sensations to become 'unpleasant.' Knudsen (33) reports that vibrations of 64 cps in frequency and 0.235 cm. in amplitude become painful to the fingertip. Reiher and Meister (1) point out that there is no single relationship to human appreciation as to 'pleasantness of sensation' of any one vibratory characteristic, namely frequency, amplitude or velocity. Schubert (7) subscribes to this thesis, but Zeller (57) contests it. Without accurate definition of their terms Reiher and Meister (1) state that vibration can exert 'physiologic effect', and they give an empirical equation expressing their results up to 0.1 cm. in amplitude and 40 cps in frequency. The variation in subjective data reckoned by different writers ranging from 'disagreeable to dangerous limits' of vertical vibration upon man is presented graphically by Lippert (58).

### *Effects of Air-transmitted Vibrations (Audible and Ultrasonic)*

1. *Audible Frequency Range.* More than 25 occupations have been recognized as etiologic agents for hearing loss (59, 60). Typical examples of this occupational disease are 'boilermakers' deafness' (61), 'weavers' deafness' (62) and the auditory loss of shoe-making machine workers (20). Recently, similar auditory defects have been correlated with the occupations of airplane engine testing (51, 64), flying of aircraft (60) and firing of various forms of ammunition (65, 66). Both acute, temporary loss of hearing (67-69) and also chronic, permanent forms of deafness (60) occur with exposure to loud noise depending, obviously, on duration of exposure as well as the intensity of the sound. Noise has its unfavorable effect not only on the auditory apparatus, but on the visual (69, 70), equilibrical (67), respiratory (71), gastro-intestinal (72) and even central nervous systems (73-75). Not all the effects of sound, in contradistinction to noise, are damaging to the organism; certain music, for example, has a soothing effect (74) which has been advantageously utilized to increase workers' production in industry (76, 77).

2. *Ultrasonic Frequency Range.* In 1927 Wood and Loomis (78) published a preliminary note regarding a piezo-electric oscillator of quartz which vibrated 300,000 times per second. Their experiments, involving exposure of various forms of life in liquid media to this apparatus, revealed that spirogyra filaments could be torn, paramecia ren-



dered immobile or killed, red blood cells rapidly hemolyzed and small frogs and fishes killed within one to two minutes. Bacteria similarly exposed to these vibrations were unaffected, presumably because they present so small a surface area. More complex organisms, namely, mice, were 'weakened' upon brief exposure to the piezo-electric oscillator. Loomis continued these observations with Harvey and Harvey (79). Soon afterward Schmitt and Uhlemeyer (80) subjected a large number of organisms to ultrasonic vibrations and reported that lethal effects were produced at the surface of the organisms by means of cavitated gas bubbles, thereby confirming the findings of Johnson (81). At the present time, modern mechanisms, such as the jet airplane engine, produce vibrations in the ultrasonic range, but adequate instrumentation for measuring such sounds is not generally available.

Some examples of the effects of audible and ultrasonic frequencies upon man and upon lower organisms, as published by different authors, are summarized in tables 3 and 4.

The mechanism by which noise produces damage involves transmission of sound to the inner ear both by air and by bone conduction (20, 86). The cochlea is so constructed anatomically that the site of histologic damage depends upon the frequency (90). The hearing tone loss is invariably above the predominant frequency of the offending noise (69, 5). Sudden blast pressure against the eardrum, resulting, for example, from unprotected exposure to artillery fire, is uncommonly involved in production of permanent deafness (49, 91). The minimum intensity causing auditory impairment, after protracted periods of exposure, is roughly 70 db (50, 64). The greatest incidence of deafness, as noted in groups of workers studied at random, occurred upon long exposure to noisy intensity levels of 80 to 90 db (82). An intensity of about 120 db is generally regarded as the level at which sound is 'felt' (53) but it is not until 130 db that noise becomes painful (59). There is wide individual sensitivity to noise (49). Only certain forms of mental performance are disturbed by noise (5, 75). By virtue of the concomitant influence of other annoying factors usually accompanying exposure to noise, Stevens (92) adjudges that noise exerts very little effect on most types of mental, motor and physiological activity, although he concedes that noise as a subjective experience is disagreeable and tiring.

#### *Indication for Experimental Study with Jet Engine*

The exigent need for a solution to the question of the effect of turbo-jet engine vibrations upon man led us to conduct preliminary tests involving the exposure of human test subjects, rather than lower animals, to a jet engine of which the mechanical characteristics were thoroughly understood and controlled. The General Electric I-16 turbo-jet engine met these qualifications and was further suited to our purpose by virtue of its generating relatively low power compared with other present-day jet engines and with those

predicted for the near future. Considering both medical and military features of the problem, the following experiments were performed.

#### MATERIALS AND METHODS<sup>4</sup>

*Description of Equipment.* A General Electric I-16 turbo-jet engine mounted on a rigid steel test stand was used as the source of vibration in this study. This engine, using gasoline as fuel, develops a thrust of 1200 pounds

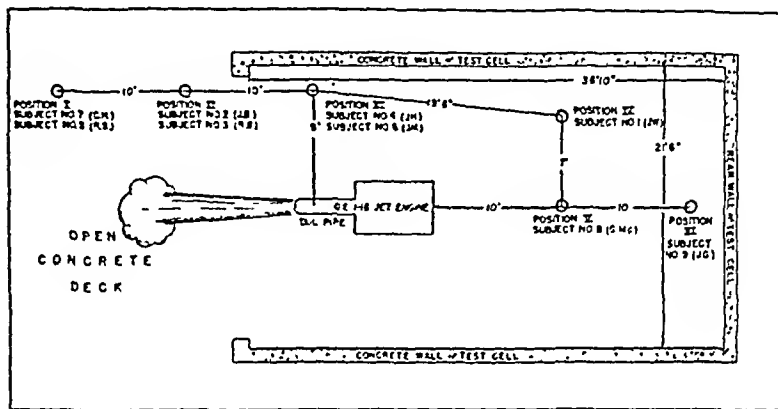


Fig. 1. SCHEMATIC REPRESENTATION of position of jet engine in the test cell and the spatial relationship of the human experimental subjects to the engine.

at its normal operating speed of 15,000 rpm. The test stand was bolted to the concrete deck and located near the open door of a test cell. The test cell, formed of concrete deck, walls and ceiling, measured 33 feet in length, 22 feet in width and 35 feet in height. The engine was so located that 9 feet of space existed on either side of the test stand; the after end of the exhaust pipe was 3.75 feet from the open deck and the forward portion of the engine was 24 feet from the solid, closed wall of the test cell.

On one side of the engine, 9 volunteer Navy enlisted men were assigned positions to simulate the likely sites where ground crew personnel and pilot would be located in relation to such an engine installed in an airplane. Figure 1 illustrates diagrammatically the positions of the engine and the test subjects.

The engine was run by an experienced crew at a constant speed of 15,000 rpm for one hour daily during the first 10 days of the experiment and for two consecutive hours daily during the last 5 days of the experiment, comprising

<sup>4</sup> The physical equipment employed in these experiments was provided under the auspices of the Aero Medical Equipment Laboratory, Naval Air Materiel Center, U. S. Navy Yard, Philadelphia, Pa. Technical measurements, other than clinical determinations, were performed by appropriate laboratories of this command. The facilities of the U. S. Naval Hospital, Philadelphia, were most generously placed at the disposal of the writers.

a total of 20 hours of exposure of the test subjects during the 6-week experimental period. For the purpose of determining the frequency spectrum of the engine noise, sound analyses were made by means of General Radio Sound and Wave Analyzers, a General Radio Sound Level Meter, and WCA-2 Sonar Receiving Equipment. Vibration analyses of amplitude and frequency generated at different positions of the concrete deck by the operating jet engine were made by means of a General Radio Vibration Meter and General Radio Vibration Analyser. Analyses of the exhaust gases

TABLE I. MECHANICAL VIBRATORY EFFECTS UPON MAN

VIBRATING DEVICE	EFFECT ON MAN	EVIDENCE	REFERENCE
'Rotary air-driven tool'	Percussion neuritis of hands ('dead hand')	Personal exper. with patients	(18)
Pneumatic hammer	Raynaud's disease and scleroderma	Case history	(19)
Pneumatic hammer	Bone cysts	Review of literature	(13)
Shoemaking machines	'Vasoneurotic diathesis' of hands	Cites references	(20)
Airplanes in flight	'Kidney ailments'	None given	(21)
Vibrating platform	Temporary decr. in visual acuity; loss of patellar reflex	Exper. by author	(2)
Vibrating platform	Temp. incr. in resp. rate with decr. vol. of resp. Decr. in b. p. and incr. in pulse rate	Exper. by author	(4)
'Vibrating stimuli'	Temp. incr. in fetal heart rate	Exper. by author on pregnant women	(22)
'Vibratode'	'Physiotherapeutic panacea'	Personal experience with patients	(23)

were made at the tailpipe of the engine and along the exhaust stream. Daily records were kept of ambient temperature and humidity, and periodic readings were made of the ambient temperature at the positions occupied by the test subjects.

*Choice and Examination of Human Test Subjects.* Prior to accepting volunteers for experimental exposure to the operating jet engine, thorough medical histories and physical examinations were made of each candidate. Only physically sound subjects, free of any suspicious anamnesis, were approved. Two of the men selected as test subjects were found to present certain emotional instabilities and were invited to participate because of, rather than in spite of these findings, since these men could be regarded as potentially 'susceptible individuals' to suggested illness. The test subjects, ranging in age from 19 to 21 years, were given careful fluoroscopic and x-ray chest studies, and also 5-hour upper gastro-intestinal visualizations (using orally ingested barium) before the experiment was begun and when it was

finally terminated. Similarly, before the commencement of the experiment, complete audiometric tests were performed, including monaural and binaural speech-reception hearing tests, conversational and whispered voice tests, and Rinne, Weber and Schwabach tests. During each day of exposure to the jet engine, audiograms were made of all subjects, and when indicated by hearing loss, other of the above-mentioned hearing tests were performed. At the end of the entire experiment, final audiographic tests were conducted. Using Snellen charts, tests of visual acuity were made before

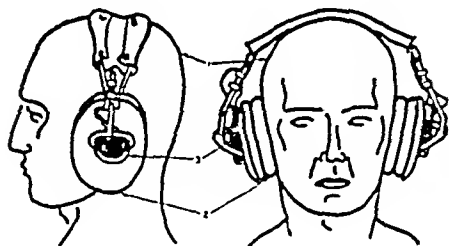


Fig. 2. EAR PROTECTOR ASSEMBLY. 1) Pilot's leather helmet; 2) double kapoc-filled 'doughnut'; 3) earphones.

and after the experiment. At random intervals, during both one and two-hour periods of operation of the jet engine, electrocardiographic and electroencephalographic recordings<sup>5</sup> were made. During the course of the experiment, basal metabolic studies were done on each subject on two occasions, just as he awakened from a night's rest. During the 5 days of two-hour exposures to the engine, the total volume of daily urinary output was measured. Pre-experimentally, in addition to the physical examination of all test subjects, the following laboratory tests were performed: (a) complete blood count; (b) urinalysis, including specific gravity, pH, tests for sugar and albumin and microscopic examination of the centrifuged sediment; (c) kidney function test, using phenolsulfonephthalein given intravenously; (d) fasting blood sugar level (method of Folin and Wu); (e) icteric index; (f) sedimentation rate (method of Wintrobe); (g) hematocrit; and (h) bleeding and clotting times.

When laboratory and other tests were made on the medical officer (A. F.) these data are included and thus provide results for 10 test subjects.

#### OUTLINE OF EXPERIMENTAL ROUTINE

The schedule of a typical experimental day was as follows: at about 8:00 a.m. the subjects were seated for 10 minutes so that blood pressure, pulse, temperature and respiratory rate could be measured. Each man then assumed his regularly assigned

<sup>5</sup> It was found that electroencephalographic recordings free of distortion could be made on the test subjects during the operation of this engine without shielding of the electroencephalographic equipment against other than radio interference. However, this could not be done in the vicinity of a more powerful jet engine (TG 180) because of vibratory interference.

position, with ears protected, where he could either stand, or sit on an all-metal chair while the engine was run for the prescribed period at 15,000 rpm. (The men commonly drowsed, or read magazines during the test period.)

While the engine was in operation, the medical officer (*A. F.*) moved about the different positions among the test subjects and measured temperature, pulse and respiration every 15 minutes. Occasionally blood pressure readings were taken by palpation of the radial artery and reading of an aneroid sphygmomanometer gauge—a method admittedly inaccurate for diastolic pressure, but nevertheless the only one that could be used under the circumstances. Each man was observed closely for neurological and psychological reactions during the engine run. At 15 to 30-minute intervals simple neurological tests such as tendon reflexes (biceps and patellar), Romberg, adiodochokinesis and heel-to-knee localizations were made on each test subject. Immediately after the engine was turned off, blood pressure, temperature, pulse and respiratory rates were recorded each day by the same observer, an individual who had not been exposed to the engine. The men then walked about 100 yards to the laboratory where they voided a specimen of urine. Fingertip blood was taken from each test subject for complete blood counts. When special tests (such as icteric index, sedimentation rate, etc.) were desired, blood was drawn from an antecubital vein at this time. When blood sugar studies were done no breakfast was permitted and the samples of blood were drawn in the morning, before and after the test subject was exposed to the engine. Following collection of these specimens for laboratory study and following questioning as to their subjective reactions to the engine run, the men went to lunch.

From 1:00 to 3:00 p.m. audiometric tests were made. During this time further questioning and physical examination of each man was done. Special attention was given to neurologic tests and to otoscopic inspection of the ears. The test subjects were usually dismissed at 4:00 p.m. and no limitations were imposed as to their extra-curricular activities. A minimum of 6 hours of sleep was advised, but this counsel was not always heeded. At times 'hang-overs' were to be contended with as disturbing factors in these 'un-controlled subjects'.

*Ear Protective Equipment.* By experience, it was found that water- or mineral oil-moistened cotton plugs placed in the external auditory canals and used in conjunction with standard pilots' leather helmets and earphones fitted with a double kapok-filled 'doughnut' provided the most convenient and satisfactory form of ear protection against the noise of the jet engine. This protective assembly, illustrated in figure 2, was used throughout the latter 15 hours of the experiments by all test subjects.

## RESULTS

### *Negative Findings*

Since *negative* findings predominate in the clinical observations, mention is first made of these. There was no change noted in the general physical condition of these men upon daily examination during the course of the experiment. The simple neurologic tests that were made were nor-

mal, as were the values for pulse rate, respiratory rate and blood pressure obtained before, during and after the daily exposure to the engine. It is pointless to itemize these normal figures, or those for visual acuity, electrocardiographic and electroencephalographic pattern. Normal basal metabolic rates were maintained during the experimental period. X-ray findings of the chest and gastrointestinal tract were not remarkable. Further, there is no need to cite the normal figures found for daily urinary output, nor daily

TABLE 2. MECHANICAL VIBRATORY EFFECTS ON ANIMALS<sup>1</sup>

VIBRATING DEVICE	EFFECT ON ANIMAL	SPECIES OF ANIMAL	REFERENCE
Vibrating rod	Vibrations to whole nerve of tooth	Cats	(24)
Vibrating box	Decr. in body wt. and eventually death	Rabbits, rats	(25)
Vibrating box	Delay of wound healing	Mice	(26)
Vibrating box	Incr. in b. p.	Rabbits	(27)
Vibrating box	Slow rise in body temp.	Rabbits	(28)
Vibrating platform	No abnormalities in dentition	Rats	(29)
Vibrating rod	Loss of patellar reflex upon stim. of femoral artery	Cats	(3)
Vibrating table	Pathological degen. of structures of internal ear	Rabbits	(30)

<sup>1</sup> Evidence in all cases was from experiments.

urinalyses, phenolsulfonephthalein kidney function tests, sedimentation rates, bleeding and clotting times and icteric indices. Inconsistent values for hematocrit suggest laboratory error and are regarded as worthless. However, despite normal values for daily blood counts, it is of interest to list representative figures; these comprise table 5. Also included in this table are fasting blood sugar values, concerning which some comment will be made.

### *Positive Findings*

*Blood Values.* From the foregoing figures, it is to be seen that although a slight drop in red blood count appeared during the first two days of the experiment in 6 of the 9 test subjects, this decrease was not accompanied by a fall in hemoglobin nor an elevation of icteric index, and no blood was found in urine or stools. During the one-hour period of engine operation the fasting blood sugar values became higher in all cases than the pre-exposure level by 3-28 mgm/100 ml., an average rise of 16 mgm/100 ml. However, after the 2-hour period of engine operation, there was a fall in 7 of the 9 test subjects in fasting blood sugar values below the pre-exposure level by 7-52 mgm/100 ml., an average fall of 33 mgm/100 ml.

*Auditory Data.* A striking decrease in auditory acuity was noted on the first two days of exposure to the engine both subjectively and objectively

TABLE 3. EFFECT OF SOUND UPON MAN

SOUND SOURCE	OCCUPATION AFFECTED	EFFECT ON MAN	EVIDENCE	REFERENCE
Riveting presses	Press operators	Eventual permanent high tone deafness	Not specified	(81, 82)
Shoemaking machines	Machine operators	" "	References	(20)
Airplane engine test cell	Testers	" "	Cases observed	(50)
" "	"	'Gastropathies'	" "	(51)
Airplane in flight	Pilots	Eventual permanent high tone deafness	Study conducted	(64)
" " "	"	" "	" "	(60)
Boilermaking equipment	Boilermakers	" "	References	(61)
Large calibre guns	Sailor-gunners	Acute trauma to eardrum and some chronic hearing loss	Cases observed	(66)
Weaving looms	Weavers	Eventual permanent high tone deafness; impaired work productivity	References	(62)
Street noises	Residents of New York City	'Emotion'; incr. in rate of degeneration of heart and arteries	Survey	(83)
Audiometer-amplification unit	Test subj.	Decr. in rate of stomach contractions	Study conducted	(72)
Telephone receivers	" "	Decr. in visual acuity	" "	(69, 70)
Pure tones of high intensity	" "	Dizziness, nausea, sweating	" "	(69)
Pure tones of high intensity	" "	Temporary diplacusis and hearing loss	" "	(69)
" "	" "	Incr. in general fatigue	" "	(5)
Airplane in flight	Pilots	Incr. in general fatigue	" "	(84)
Simulated office noise	Test subj.	Decr. in efficiency; incr. in energy consumption	" "	(76)
Recorded music	Factory workers	Incr. in workers' production	Survey	(74)
" "	Test subj.	Reinforces patellar reflex	Study conducted	(37)
Turbo generator	" "	Ultrasonic: 'Eyes out of focus; muscles jerk; jaw drops'	Personal observation	

<sup>1</sup> Unless otherwise indicated, the sound was in the audible frequency range.

as revealed by the audiogram and by tests of reception of conversational and whispered voice. A composite audiogram<sup>6</sup> of *Test Subject No. 4* (J. H.) who was located at Position III (fig. 1) is presented in figure 3 as illustrative of the most marked effect.

The men located at Positions I, II and III, i.e., those to the side of and behind the exhaust pipe, suffered the hearing losses indicated above, as did

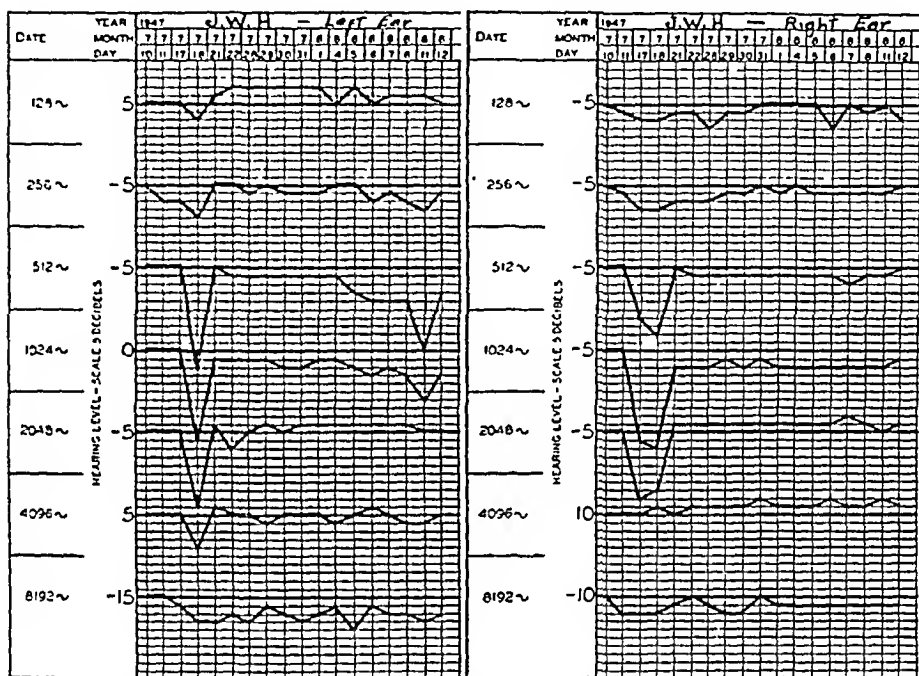


Fig. 3. COMPOSITE AUDIOGRAM of *Test Subject 4* (J. H.) illustrating reversible hearing loss in the 'conversational frequency range' 512 to 4096 cps that occurred upon first exposure to the jet engine.

the medical officer, despite the use of rubber plug ear defenders made by the Mines Safety Appliance Company ('V-51-R Ear Wardens'). It is noteworthy that the reversible hearing loss occurred in the frequency range 512 to 4096 cps, namely, that in which ordinary conversation falls. It was noted subjectively by those who had suffered hearing losses that auditory acuity was fully regained within 12 hours after cessation of exposure to the engine. The test subjects located forward of the engine (Positions IV, V and VI) showed negligible hearing losses. After consistent and proper use of the ear protective assembly shown in figure 2, practically no hearing losses occurred

<sup>6</sup> This audiogram was most kindly furnished by Miss E. Thompson, of the Aural Rehabilitation Clinic, U. S. Naval Hospital, Philadelphia. She plans to publish the audiological aspects of this study in a separate paper in the near future.



in any test subject, regardless of the position he occupied in reference to the jet engine. It was found by audiometric studies (including monaural and binaural speech reception and audiographic performance tests) that this ear protective assembly accomplished a damping of 25 to 35 db of loud noise. In this capacity the assembly was more effective at the higher frequencies and less so at the lower frequencies.

TABLE 4. EFFECT OF SOUND UPON LOWER ORGANISMS

TYPE OF SOUND	EFFECT ON ORGANISM	ORGANISM	EVIDENCE	REFERENCE
Noise	Damage to cochlea	Guinea pigs	Histologic	(61)
Noise	" " "	" "	"	(85)
Noise	" " "	Mice	"	(86)
Noise (low freq.)	Audiogenic epileptoid seizures	Rats	Observation	(87)
Ultrasonic <sup>1</sup>	Cerebral lesions	Dogs, cats, monkeys	Gross and histologic	(88)
"	Death	Frogs	Observation	(78)
"	"	Fish	"	(78)
"	Temporary weakness and immobility	Mice	"	(78)
"	Cellular disruption	Spirogyra	"	(78)
"	Death	Protozoa	"	(81)
"	Inactivation	Viruses	"	(89)
				(80)

<sup>1</sup> Transmitted through liquid medium.

*Psychosomatic Responses.* Seven of the 10 test subjects reported that they were more tired and/or more irritable during the course of the experiment than usual. These reactions were observed both subjectively and also by friends. Loss of weight varying from 5½ pounds (*Subject 6*) to 19 pounds<sup>7</sup> (*Subject 5*) was found in 5 men, whereas 5 subjects lost no weight at all. The two test subjects originally considered emotionally unstable advanced the bizzare claims of increased rate of growth of hair on face, arms and legs during the experiment; this contention could not be verified objectively. No change in sexual desire or potency was reported by any test subject during and after the experiment.

### Noise Spectrum Analysis

Preliminary analyses of the noise produced by the engine in operation at 15,000 rpm revealed average overall sound levels of about 120 db up to a frequency of 7500 cps at the positions occupied by the test subjects. Meas-

<sup>7</sup> These weight losses are believed to reflect improper food habits of the subjects concerned, rather than an adverse effect of the jet engine upon them.

urements made in a range from 20 cps to 38,000 cps by use of a General Radio Sound Level Meter and General Radio Sound and Wave Analyzers at a level of  $5\frac{1}{2}$  feet above the deck in the various exposure positions disclosed peaks at frequencies of 7300, 9300, 13,500, and 14,500 cps. The intensity levels were low at the lowest frequencies, namely, about 81 db at 50 cps, rose to shallow peaks of 90 to 100 db in the frequency range of 200 to 800 cps and leveled off in plateaus of 80 to 90 db intensities in the frequency range of 700 to 2500 cps. By using the Sonar Receiving Equipment, the presence

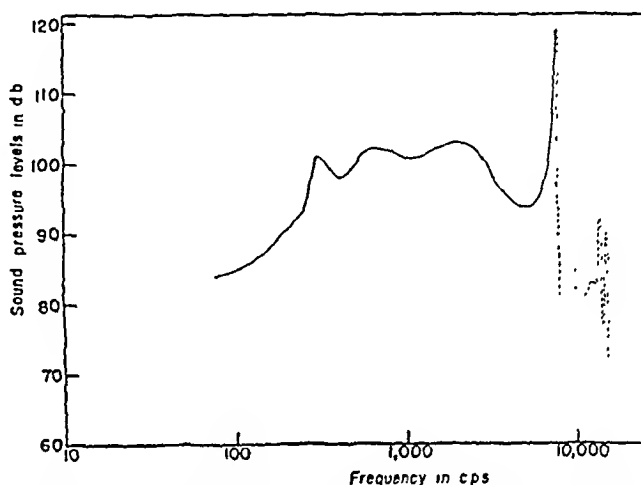


Fig. 4. ANALYSIS OF NOISE at Position III (cf. fig. 1) produced by jet engine operating at 15,000 rpm.

of peaks was noted at 21,700, 27,400 and 29,600 cps. Incomplete calibration data above 7500 cps make uncertain the exact intensities of the sound beyond this frequency. Figure 4 exemplifies graphically these measurements of the engine noise prevailing at Position III.

### *Vibration Analysis*

By means of a General Radio Vibration Meter and a General Radio Vibration Analyzer, determinations were made of the vibrations generated in the concrete deck aft of the engine that was operating at 15,000 rpm. These measurements, made at Positions I and II, covered the range from 100 to 750 cps. It was found that the vibrations were very complex in form and very difficult to analyze. Further data are required before thorough evaluation of the results is possible. However, it suits the present purpose to list some typical figures for vertical accelerations and velocities found at Position II. These vibration values comprise table 6.

TABLE 5. BLOOD DETERMINATIONS DURING COURSE OF EXPOSURE TO JET ENGINE

TEST SUBJECT	DATE <sup>1</sup>	ENGINE IN OPER- ATION	BLOOD COUNT			DIFFERENTIAL CELL COUNT						FASTING BLOOD SUGAR		
			HGB	RBC	WBC	Seg.	Non seg.	L	M	E	B	Before	1 hr. after	2 hr. after <sup>1</sup>
			gm.	1X10 <sup>6</sup>	1X10 <sup>3</sup>							mgm/100ml.		
1 N. W.	7-17	I	15.5	5.09	5.9	68	2	29	I	0	0	96	124	
	7-18	I	15.5	4.96	5.5	61	2	32	3	2	0			
	7-28	I	15.5	5.22	6.1	58	0	32	4	2	2			
	8-7	2	15.0	5.10	5.6	70	0	29	I	0	0			
	8-8	2	15.0	5.13	7.4	59	2	37	I	2	0	125 <sup>2</sup>		96
2 J. B.	7-17	I	15.5	5.45	7.8	51	0	44	4	0	I	72	98	
	7-18	I	15.5	5.10	8.3	55	0	43	2	0	0			
	7-28	I	15.5	5.37	6.6	54	0	43	I	I	I			
	8-7	2	15.5	5.35	7.5	56	I	42	I	0	0			
	8-8	2	15.5	5.29	7.3	53	0	45	I	0	I	105 <sup>2</sup>		71
3 R. B.	7-17	I	14.0	5.10	6.8	62	2	35	I	0	0	73	80	
	7-18	I	14.0	4.71	7.0	71	I	28	0	0	0			
	7-28	I	14.0	4.96	5.9	53	I	43	2	I	0			
	8-7	2	14.0	4.85	8.3	56	0	42	0	I	I			
	8-8	2	14.0	4.87	7.7	64	I	34	0	0	I	104 <sup>2</sup>		91
4 J. H.	7-17	I	14.0	4.49	8.4	50	2	44	I	I	2	80	100	
	7-18	I	14.0	4.42	7.3	61	2	35	I	I	0			
	7-28	I	14.0	4.41	6.1	46	2	48	3	0	I			
	8-7	2	14.5	4.85	6.1	53	0	44	I	2	0			
	8-8	2	14.5	4.79	5.6	61	0	35	3	I	0	86 <sup>2</sup>		93
5 R. S.	7-17	I	14.5	4.72	5.3	64	2	31	3	0	0	76	94	
	7-18	I	14.5	4.80	7.2	69	2	26	3	0	0			
	7-28	I	14.5	5.00	7.8	60	I	34	3	0	2			
	8-7	2	14.5	4.98	5.8	66	0	31	2	0	I			
	8-8	2	14.5	4.85	6.7	62	0	34	I	3	0	83 <sup>2</sup>		83
6 J. M.	7-17	I	14.5	4.75	8.6	37	0	61	I	0	I	84	98	
	7-18	I	13.5	4.47	6.5	47	0	52	I	0	0			
	7-28	I	13.5	4.60	6.7	46	I	50	2	I	0			
	8-7	2	14.0	4.46	8.0	43	I	53	I	I	I			
	8-8	2	14.2	4.65	7.6	35	0	63	2	0	0	116 <sup>2</sup>		78
7 C. H.	7-17	I	14.5	4.65	7.6	66	I	29	4	0	0	80	88	
	7-18	I	14.5	4.97	10.6	63	4	30	2	I	0			
	7-28	I	14.0	4.65	7.4	64	4	29	3	0	0			
	8-7	2	14.5	4.90	12.3	68	I	30	I	0	0			
	8-8	2	14.5	4.92	7.4	60	2	38	0	0	0	118 <sup>2</sup>		72
8 G. Mc.	7-17	I	14.0	4.46	6.8	51	2	42	3	0	2	89	92	
	7-18	I	14.5	4.98	7.0	55	I	40	4	0	0			
	7-28	I	14.5	4.74	5.9	58	2	33	5	0	2			
	8-7	2	14.5	4.92	6.7	60	2	35	I	2	0			
	8-8	2	14.5	4.94	7.8	63	I	36	0	0	0	95 <sup>2</sup>		78

TABLE 5—Continued

TEST SUBJECT	DATE <sup>1</sup>	ENGINE IN OPERATION	BLOOD COUNT			DIFFERENTIAL CELL COUNT						FASTING BLOOD SUGAR		
			HGB	RBC	WBC	Seg.	Non seg.	L	M	E	B	Before	1 hr. after	2 hr. after <sup>2</sup>
		hr.	gm.	$1 \times 10^4$	$1 \times 10^4$							mgm/100ml.		
9 J. G.	7-17	1	15.0	5.20	5.6	43	2	51	3	0	1	82	106	
	7-18	1	14.5	4.97	7.9	60	0	39	1	0	0			
	7-28	1	14.5	4.97	5.8	62	2	32	4	0	0			
	8-7	2	14.5	4.83	7.2	61	0	36	1	0	2			
10 A. F.												123 <sup>2</sup>		71

<sup>1</sup> The dates listed are the first two days of the experiment, one intermediate day and the final two days.

<sup>2</sup> Because a different laboratory performed the blood sugar analyses recorded for the 2-hour exposure period, the absolute values differ rather markedly from those of the 1-hour exposure period. However, relative to the particular experimental condition, comparison of figures in any column is feasible.

### Exhaust Gas Analysis

Gas analysis of the exhaust stream of this engine revealed only traces of aldehydes, 0.015 per cent carbon monoxide, 2.1 per cent carbon dioxide and 17.4 per cent oxygen.

### Environmental Temperature and Humidity

During the 15 days when experiments were conducted the external environmental temperature varied from 71° to 87°F., with an average value of 78.4°F. as recorded by the dry bulb thermometer. The relative humidity ranged from 46 to 96 per cent, with an average value of 61.3 per cent. The temperature measurements at Position I, II, IV, V, and VI (fig. 1) were regularly within 1° to 2° of the external environmental temperature, while Position III occasionally became 3° to 4°F. warmer than the outside temperature.

### DISCUSSION

Since the purpose of the experiments undertaken in this study was to provide promptly information pertaining to gross clinical response to vibrations emanating from a jet airplane engine operating at high speed, no pre-text is made of completeness. However, some of the channels toward which future study may profitably be directed are indicated from the present observations and to this extent, if nothing else, these predominantly negative findings are timely and of value.

Just how noise and vibration exert an untoward effect upon man is not fully known. Spiegel (93) describes the labyrinthine stimulation of the

sympathetic nervous system of animals and man. Davis *et al.* (69) have observed dizziness, sweating, nausea and loss of balance in the course of their experiments on exposing human subjects to pure frequency tones of high intensity.<sup>8</sup> Spooner (73) adds that noise causes fatigue mainly of the ears, which gradually extends to the whole nervous system, thereby inducing greater fatigue than would muscle weariness. Coermann (50) explains the phenomenon of noise-induced fatigue as the end result of successful competition by noise against other impulses that simultaneously enter the cerebrum; the greater mental concentration necessary to apprehend the desirable impulses involves excess expenditure of energy and leads to rapid fatigue. Reiterating Coermann's (50) point, McFarland (5) also enumerates the physiological and psychological influences of noise.

That adaptation of the body occurs both to vibration (8, 46) and to noise (20, 62, 73) is well known. With reference to vibratory effects on the organism, von Békésy (55, 56) studied the human body from the point of view of its damping efficiency as a mechanical system and found that skin and muscle have high impedences in contrast to the relatively little protection against vibration afforded the head by the cervical vertebrae.

The foregoing considerations have bearing upon the interpretation of our experimental findings. First, we were able to get noise levels from our jet engine corresponding in intensity with those which Dickson (94) measured in a 'Meteor III' aircraft in flight and a 'Vampire' on the ground. Both Dickson's and our studies assumed the symmetry of a jet airplane as nice enough to validate unilateral sound measurements. Although Dickson did find that the noise intensities were similar on the ground and in the air, it is permissible to apply these results only to ground crew personnel. It cannot be inferred that similar effects accrue to the pilot during flight, albeit reasonable enough to suppose this to be the case.

Secondly, the audiometric findings on our subjects showed results similar to Davis' (67), in temporary auditory loss upon exposure to noise of intensity of 120 to 130 db and gradual recovery. In line with Davis' (68) results, we found that airplane noise, a band-spectrum type of noise, did not cause diplacusis in our subjects. Despite peaks in the audible noise spectrum in our experiments at 7300, 9300, 13,500 and 14,500 cps we did not find hearing loss in the high frequency range. These negative findings do not preclude the possibility that some degree of adaptation to both vibration and noise may have occurred in our test subjects, but this appears unlikely or, at best, of minor significance. Thirdly, ultrasonic energy is generated by the jet engine used in our experiments and although not accurately meas-

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<sup>8</sup> It is of passing interest to note that the experiments of Davis and his co-workers (69) differ from those of the present paper not only in our use of *noise* as a sound source but also in our exposing test subjects on *successive* days and in our doing *daily* audiograms.

ured for want of satisfactory instrumentation, it may be reasonably concluded that no deleterious effect of clinical significance occurs under these experimental conditions. The physical and psychological reactions observed in our test subjects are well within the limits of expected response to audible noise and to vibration.

No change in visual acuity was noted subjectively or objectively in our test subjects either during or after the experiment. Coermann (2) reported no ill effects other than slightly decreased visual acuity, described as 'purely mechanical', after exposing his human volunteers on a vibrating platform for 2 to 8 hours. He observed also a decrease in the knee-jerk reflex.

With regard to diminution of patellar reflex it was questionable that this response was to be anticipated in the present experiment, since our vibrational amplitudes and frequencies were not great. We did not find any patellar or biceps reflex changes. Doubt as to the occurrence of patellar reflex diminution was cast by Sommer (95) who sought to learn whether individual muscle fiber contractions occurred with each vibratory impulse, such as Coermann (2) had applied to his subjects. He vibrated the lower arm of a test subject at 32 to 37 cps for 30, 60 and 90 minutes and by measuring muscle action currents learned that the biceps does not fatigue even with 200,000 successive stretch reflexes. It is to be noted, however, that this evidence of Sommer (95) is considerably weakened by his failure to state the amplitude of vibration used in his experiments. Quite aside from any dispute as to occurrence of this change in muscle reflex, the phenomenon would not appear to bear any practical significance under ordinary working conditions.

The test subjects of the present experiment did not exhibit unusual bodily tension when the engine was turned up, and certainly did not show any abnormal muscular relaxation shortly thereafter, as Coermann (2) observed within 5 minutes after onset of severe vibration in his test subjects. Nonetheless, some evidence of subconscious tenseness in our test subjects may be gleaned from the rise of 3 to 28 mgm/100 ml. in fasting blood sugar after one hour of exposure to the engine and a fall of 7 to 52 mgm/100 ml. after two hours of exposure. The one-hour rise may be attributed to the temporary hypoglycemia induced by adrenalin, whereas the two-hour fall would represent utilization of the available blood sugar, resulting in a temporary, relative hypoglycemia. As an alternative hypothesis, an adrenocorticosteroid hormonal response in an 'alarm reaction' could be considered in explanation of the blood sugar changes. Although no control subjects, sitting for one to two hours in a quiet environment, were studied for blood sugar fluctuations, it remains unlikely but possible that the blood sugar changes observed in this experiment are more apparent than real.

Brief mention is to be made as to the rationale underlying our cursory

investigation of the gastrointestinal tract. We did not attempt to record gastrointestinal motility, as did Smith and Laird (72) in their study of the effect of loud noise on stomach contractions. We planned to make x-ray studies during the course of the experiment when and if symptoms referable to gastrointestinal tract appeared. None was forthcoming, and we were content to accept as gross evidence the normal patterns of stomach and upper intestinal motility seen fluoroscopically and by x-ray film. The explanation made by Smith and Laird (72) for their findings of 37 per cent decrease in the number of stomach contractions per minute in response to 80 db of noise

TABLE 6. VERTICAL VIBRATION OF CONCRETE DECK AFT OF JET ENGINE OPERATING AT 15,000 RPM (POSITION II)

FREQUENCY <sup>1</sup>	ACCELERATION <sup>1</sup>	VELOCITY <sup>1</sup>	AMPLITUDE <sup>2</sup>
cps	in./sec. <sup>2</sup>	micro-in./sec.	cm.
100	0.0	200	$8.2 \times 10^{-7}$
200	0.5	300	$7.27 \times 10^{-7}$
250	3.0	2500	$4.15 \times 10^{-6}$
260	—	800	$1.25 \times 10^{-6}$
300	0.5	300 <sup>2</sup>	$3.82 \times 10^{-7}$
400	—	100	$1.01 \times 10^{-6}$
480	0.5	—	$1.49 \times 10^{-6}$
500	1.0	—	$2.7 \times 10^{-6}$
520	0.5	—	$1.23 \times 10^{-6}$
700	1.0	—	$1.38 \times 10^{-6}$
750	0.5	—	$5.96 \times 10^{-6}$

<sup>1</sup> Data obtained by measurement with General Radio Vibration Meter and Analyzer. Results expressed as peak root mean square accelerations and velocities.

<sup>2</sup> Calculated from measured accelerations and velocities by use of the following formulae: Velocity = amplitude  $\times 2 \pi f$ ; acceleration = amplitude  $\times 4 \pi^2 f^2$ . Results are average values.

as similar to a 'fear reaction' was acceptable to us; and no need was felt for confirming an established physiologic tenet.

A final word is to be mentioned regarding prophylaxis against undesirable effects of noise and vibration. Many writers agree that cotton plugs, preferably moistened, are the best and most convenient form of ear defender against noise (20, 48, 90, 96). Our experience is in line with this consensus and we are firm in our disagreement with Davis' (97) report which states that Mine Safety Appliance 'V-51-R Ear Wardens' are satisfactory ear defenders. Not only were these physically uncomfortable to the wearers, but as figure 3 of this present study shows the most severe hearing loss occurred in this test subject as well as in the other men when this rubber device was used. Since we obtained best results by use of pilot-type leather helmet and earphones in conjunction with the moistened cotton ear plug, we favor and advocate the use of this entire assembly during prolonged exposure to noise above

100 db in intensity. Kipp (64) and Coermann (50) are likewise proponents of such a protective assembly. It does not appear that this outfit is too cumbersome nor inconvenient for workers to object to its use.

In regard to prevention of vibratory ill effects, it is impractical to have workers wear abdominal binders as Müller (4) suggests. Moreover, it is not apparent that any indication exists for abdominal defense. Wearing shoes with rubber soles (96) and, even better if feasible, sitting on cushioned seats (4) when working near a strongly vibrating floor are sensible. The most reasonable of prophylactic suggestions comes from McFarland (5) who recommends that engineers become aware of vibrations as a source of fatigue and seek to reduce these annoying vibrations during the design and manufacture of the particular mechanical equipment. Referring specifically to vibration tolerance limits in passenger aircraft, McFarland (5) recommends a maximum amplitude of 0.002 inches at a frequency of 20 cps.

#### SUMMARY

A review is made of the literature pertaining to the influence of mechanically transmitted and airborne vibrations upon man and lower organisms.

Experimental data derived from exposing 9 volunteer Navy enlisted men and a medical officer at various positions near a General Electric I-16 turbo-jet engine for a total of 20 hours over a period of 6 weeks revealed the following: *a*) Increase in fatigue and irritability during the entire course of the experiment in 7 of the 10 subjects. The others noted no change. *b*) Early, temporary, sharp decrease in auditory acuity in the 'conversational frequency range' of 512 to 4096 cps. Normal hearing was gradually regained by the 7 subjects affected within 12 hours or less after onset. *c*) Loss in weight of  $5\frac{1}{2}$  to 19 pounds in 5 of 9 subjects. It is questionable that this finding is a result of the experiment. *d*) Rise in fasting blood sugar during a one-hour period of exposure to the jet engine in all subjects and decrease in the fasting blood sugar level after a two-hour exposure in 7 of the 10 test subjects. *e*) Normal findings, unchanged from pre-experimental values, were noted for blood counts, urinalyses, kidney function tests, bleeding and clotting times, icteric indices, upper gastrointestinal x-ray studies, electrocardiograms and electroencephalograms during and after the experiment.

Noise analyses of this engine revealed overall intensities of 120 db to 7500 cps, and peaks of sound were noted up to 38,000 cps. The equipment for measuring ultrasonic frequencies is not accurately calibrated as yet. Vibration analyses of the concrete deck in which the engine generated such motion included a frequency range of 100 to 750 cps and revealed amplitudes up to  $5.96 \times 10^{-6}$  cm. in order of magnitude.



Gas analyses of the engine's exhaust stream revealed no noxious gases to be present in dangerous amounts.

A helmet-carphone-cotton plug assembly as prophylaxis against hearing loss from prolonged exposure to noise is described. This assembly reduces the noise level by 25 to 35 db, being more efficient at higher than lower frequencies.

The relationship of these experimental data to those of other workers is discussed.

The authors are pleased to express their deep gratitude for the invaluable assistance rendered them by the enlisted men who volunteered as test subjects and who were supervised by Eric Taylor, HMC; by Comdr. E. L. Corey, MSC, USNR, Professor of Physiology of the University of Virginia; by Mr. E. S. Mendelson and Mr. A. T. Kornfield, of the Aero-Medical Equipment Laboratory; by Miss E. Thompson and Staff, and by Captains A. H. Staderman and F. Harbert, MC, USN, and Comdr. T. W. Bennett, MC, USN, of the U. S. Naval Hospital, Philadelphia; and finally we thank Miss Helen Conway and her assistants of the Aero-Medical Equipment Laboratory for their clinical laboratory work.

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## *Iontophoresis with Acetyl-beta-methyl-choline and Blood Flow through the Hand at Low Environmental Temperatures<sup>1</sup>*

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THE VALUE OF ACETYL-B-METHYL-CHOLINE (ABMC) as a powerful vasodilator has been established in numerous experimental studies and therapeutic trials (1-5). Acetyl-B-methyl-choline  $(\text{CH}_3)_3\text{N}\cdot\text{CH}_2\text{CH}(\text{CH}_3)\text{O}\cdot\text{COCH}_3$ , is more stable than acetyl-choline,  $(\text{CH}_3)_3\text{NCH}_2\text{CH}_2\text{O}\cdot\text{COCH}_3$ , to which it is closely related chemically, and is devoid of the nicotinic action of the latter compound (1, 6). Since 1934, when Kovacs (7) demonstrated that choline derivatives can be introduced through the skin by iontophoresis, ABMC has been used with considerable success in the local therapy of certain vascular disorders characterized by a diminution of peripheral blood flow.

By means of an ingenious experiment in which they combined the techniques of venous occlusion plethysmography and iontophoresis, Montgomery, Holling and Friedland (8) showed conclusively that the introduction of ABMC locally results in a significant increase in the rate of blood flow through the hand. Their findings were corroborated by Abramson, Fierst and Flachs (9) who observed similar, though less marked, increases in blood flow through the forearm, leg and foot following iontophoresis of ABMC at these sites. Both of these investigations were conducted at moderate room temperatures (23° to 29°C.) and moderate to high bath temperatures (27° to 45°C.).

For several years, workers in this laboratory have been engaged in an investigation of peripheral vascular responses to different environmental temperatures and of possible methods of modifying these responses (10-14). In our experience, the intense vasoconstriction of the extremities induced by exposure to cold has been extremely difficult to overcome without removing the subject to a warmer environment. Accordingly, an investigation was undertaken to determine the effectiveness of ABMC iontophoresis in pro-

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ducing an increase in the rate of blood flow through an extremity which was initially vasoconstricted by exposure to cold. The results obtained are presented in this paper.

### METHODS

Thirty-one experiments were performed on 6 healthy young adults whose ages ranged from 18 to 29 years. All studies were conducted in a constant-temperature chamber with closed circuit ventilation and a turbulent air velocity of approximately three m.p.h. Room temperature was controlled to within  $\pm 0.5^{\circ}\text{C}$ . during any experiment.

Blood flow through the hand was determined by the venous occlusion plethysmographic method. A standard fluid-air plethysmograph, of the type used by Wilkins and Eichna (15), was modified so as to permit accurate temperature control ( $\pm 0.2^{\circ}\text{C}$ .) over a wide range ( $2^{\circ}$  to  $48^{\circ}\text{C}$ .) within the plethysmograph. This was accomplished by installing within the instrument a heating unit and a set of refrigerating coils which could be controlled either manually or by means of an electronically regulated thermostat (fig. 1).

Acetyl-beta-methyl-choline chloride (Mechoyl Merck<sup>2</sup>) was used as the fluid medium in the plethysmograph. Iontophoresis was accomplished by the method originally described by Montgomery, Holling and Friedland (8). The metal plethysmograph itself was utilized as the positive electrode. A sheet of copper screening measuring 14 x 18 inches and covered with several layers of saline-moistened gauze served as the negative electrode. The current for iontophoresis was derived from a 45 volt *B* battery and was controlled by a 10,000 ohm variable resistance. The following precautions were taken throughout the course of this study: *a*) All metal portions of the plethysmograph which might have come into contact with the extremity were carefully insulated to minimize the danger of electrical burns and for the same reason a negative electrode with a large surface area was used. *b*) An emergency knife switch was kept in the circuit within easy reach of the subject. *c*) A syringe filled with atropine sulfate, 0.75 mgm., was always kept in readiness in order to counteract any possible systemic effects of the ABMC.

Since the primary purpose of this study was to determine the effectiveness of mechoyl iontophoresis in overcoming locally the vasoconstriction produced by cold, most of the experiments were conducted at low room temperatures ( $15^{\circ}\text{C}$ .) and low plethysmograph temperatures ( $8^{\circ}$  to  $15^{\circ}\text{C}$ .).

On the day of an experiment, the subject, wearing a light cotton undershirt, light cotton shorts, fatigue trousers, light woolen socks and standard service shoes entered the test chamber and remained at rest for approximately one hour. At the conclusion of this period, thermocouples were placed on the left hand, the subject reclined comfortably in an adjustable chair and the right hand was inserted in the plethysmograph at heart level. The negative electrode was strapped securely to the subject's back and the plethysmograph was filled with a 0.2 per cent solution of ABMC at the desired temperature. Two hundred milliliters of the solution were drained off, leaving a cushion of air between the plethysmograph and the recording apparatus, although the hand remained completely covered by the ABMC. Thirty minutes were allowed for the hand to come into equilibrium with the ABMC bath, i.e., for the blood flow through the hand to reach

<sup>2</sup> Generous quantities of this drug were kindly supplied by Merck & Co.

a steady state. Basal blood flow was then determined. Each blood flow determination consisted of the average of 4 to 7 measurements taken at 30-second intervals.

The current was then turned on at approximately 2 milliamperes and was gradually increased over a period of 2 minutes until the desired intensity was reached (between 10 and 18 milliamperes, depending on the particular subject). It was kept at this level for the duration of the experiment. Blood flow determinations were made at 5- to 10-minute intervals. In most cases iontophoresis was carried out for 30 minutes, although occasionally a longer period was used. Skin temperature of the opposite hand was recorded at intervals during the experiment. In a number of cases, blood pressure and pulse rate were determined throughout the iontophoresis period.

Control studies of two types were carried out. These were: *a*) iontophoresis with normal saline instead of ABMC in the plethysmograph and *b*) blood flow determinations with ABMC in the plethysmograph but without the galvanic current. Subject reactions reported by the subject as well as any objective changes were recorded throughout each experiment.

### EXPERIMENTAL RESULTS

Under experimental conditions in which blood flow through the hand was drastically curtailed by continuous exposure to cold, iontophoresis of acetyl-beta-methyl-choline chloride usually resulted in a significant increase in hand blood flow. The results are summarized in table 1. The increase generally became apparent within 15 minutes after iontophoresis was started, reached its maximum within 30 minutes and subsided gradually after cessation of the current. There were marked individual differences in regard to the vasodilatation response. Thus, ABMC iontophoresis invariably resulted in a dramatic augmentation of hand blood flow in the case of *subject C*, while the same procedure produced only a slight effect in *subject E* (table 1). Maximum flows amounting to as much as 20 times the control flow were observed on occasion and 5 of the 6 subjects showed significant increases in blood flow through the treated hand during iontophoresis. No indirect vasodilatation in the opposite hand (as estimated by changes in skin temperature) ever occurred. Mere immersion of the hand in an ABMC bath without galvanic current had no effect on blood flow, and no significant changes were noted when current was passed through the plethysmograph filled with normal saline (table 1, fig. 2 and 3).

Prolonged immersion of the hand in either saline or ABMC at the low temperatures used invariably resulted in discomfort, amounting to severe pain in some subjects. When the galvanic current was turned on, all subjects noted 'tingling' of the hand regardless of the composition of the bath. This usually disappeared within a few minutes. In most cases, the sensations of coldness, numbness or pain were either markedly diminished or entirely absent after 15 minutes of ABMC iontophoresis and in many instances a sensation of warmth was reported. In control experiments, ionto-

TABLE 1. EFFECT OF ABMC AND NaCl IONTOPHORESIS ON HAND BLOOD FLOW AT LOW TEMPERATURES

SUBJECT	TEMPERATURE		CUR- RENT	TIME	BLOOD FLOW		REMARKS
	Room	Plethys- mo- graph			Initial	Max- imal	
Iontophoresis of ABMC, 0.2%							
A	°C.	°C.	m.a.	min.	cc./100 cc. limb tissue/min.		Hand painful, then numb during immersion in ABMC without current; 15 min. after iontophoresis had begun, hand 'comfortable'. Marked sweating for 10 hr. post-iontophoresis, confined to dorsum of treated hand.  Treated hand began to 'feel warm' 10 min. after start. Sweating on dorsum of hand for 8 hr.  Sweating on dorsum of hand for 12 hr. after iontophoresis. Pounding sensation in hand at height of ABMC effect.
	15	10	10	30	0.6	2.9	
	15	10	10	30	1.1	4.6	
	15	15	10	30	0.6	3.4	
B	15	10	10	30	0.9	2.6	Pain in hand until iontophoresis had continued for 18 min. Prolonged sweating of hand.
	15	10	10	30	0.7	2.5	Prolonged post-iontophoretic sweating.
	15	10	10	30	0.3	1.4	Prolonged post-iontophoretic sweating.
	15	10	10	30	0.7	1.8	Prolonged post-iontophoretic sweating.
	15	10	15	30	0.5	2.9	
	15	10	18	30	0.2	2.3	Pain in arm when current turned up to 22 m.a. for 1 min.
C	24	18	18	30	1.0	16.7	Hand painfully cold during saline iontophoresis and ABMC control. Felt 'warm and comfortable' after 8 min. of ABMC iontophoresis. Prolonged post-iontophoretic sweating on dorsum of hand.
	15	10	18	45	1.6	26.8	Numerous petechiae on dorsum of treated hand after iontophoresis, persisting for several days. Prolonged post-iontophoretic sweating. Throbbing sensation in hand at height of ABMC effect.
	15	10	10	30	0.6	6.8	Prolonged post-iontophoretic sweating. Hand 'comfortable' during iontophoresis. Cold before.
	15	10	18	30	0.5	20.7	Prolonged post-iontophoretic sweating.
D	15	10	10	30	0.6	3.1	Severe pain in hand during initial immersion in ABMC at 10°C., disappeared after 15 min. of iontophoresis. Prolonged post-iontophoretic sweating.

TABLE 1.—*Concluded*

SUBJECT	TEMPERATURE		CURRENT	TIME	BLOOD FLOW		REMARKS
	Room	Plethymo-graph			Initial	Maximal	
<i>Iontophoresis of ABMC, 0.2%—Concluded</i>							
<i>D (Concluded)</i>	°C.	°C.	rt.a.	rt.m.	cc./100 cc. limb tissue/min.		Throbbing sensation at height of ABMC effect. Prolonged sweating for 6-8 hr. Confined to dorsum of treated hand.
	24	15	10	30	0.7	11.7	
	30	10	10	30	0.5	4.9	
	15	10	10-15	45	0.8	5.1	
<i>E</i>	15	10	10	30	1.0	1.4	Subject complained of some nausea and dizziness after 20 min. of iontophoresis.
	15	15	10	30	0.3	1.6	Subject stated face felt 'warm' after 25 min. of iontophoresis. Sweating on dorsum of hand for 10 hr.
	30	10	10	30	1.3	3.0	Treated hand felt 'much warmer' after 15 min. of iontophoresis.
<i>F</i>	15	15	10	30	0.2	2.1	Post-ontophoretic sweating for 6 hr. on dorsum of hand. Face flushed and perspiring after 40 min. of iontophoresis. Complained of abdominal cramps.
	15	10	10	30	1.6	2.9	
	15	10	18	45	0.8	3.5	
	15	10	10	30	0.6	3.3	
<i>Iontophoresis of NaCl, 0.9%</i>							
<i>A</i>	15	10	10	30	0.6	0.8	Hand 'uncomfortably cold' throughout experiment.
<i>B</i>	15	10	10	30	0.5	0.4	Hand painful throughout experiment.
<i>C</i>	15	10	18	30	1.0	1.0	Hand painful throughout experiment.
<i>D</i>	15	10	10	30	0.8	0.8	No relief of 'cold pain' during iontophoresis.
<i>D</i>	24	18	18	30	0.7	0.7	
<i>F</i>	15	10	15	30	0.8	1.0	

phoresis of normal saline did not diminish the discomfort. As the blood flow increased during ABMC iontophoresis there was a definite increase in the amplitude of the pulse wave as recorded on the kymograph. This was often associated with a throbbing sensation in the hand.

Although much higher intensities of galvanic current have been used by other investigators (4, 8), we found that intensities greater than 20 milliamperes caused 'aching' or 'tightening' sensations in the forearms of our subjects. For this reason, the highest intensity of current utilized in these studies was 18 to 20 milliamperes. In two subjects, increasing the intensity



of current from 10 to 18 milliamperes resulted in greater increases in blood flow. Another subject, however, reacted as strongly to 10 milliamperes as to 18 milliamperes. In the few instances in which higher room temperatures and bath temperatures were used, the increases in blood flow through the hand were more marked than those seen in the same subjects at lower environmental temperatures (figs. 2 and 3).

In the great majority of cases the reaction to ABMC iontophoresis was confined to the treated hand. Systemic effects of the drug were observed

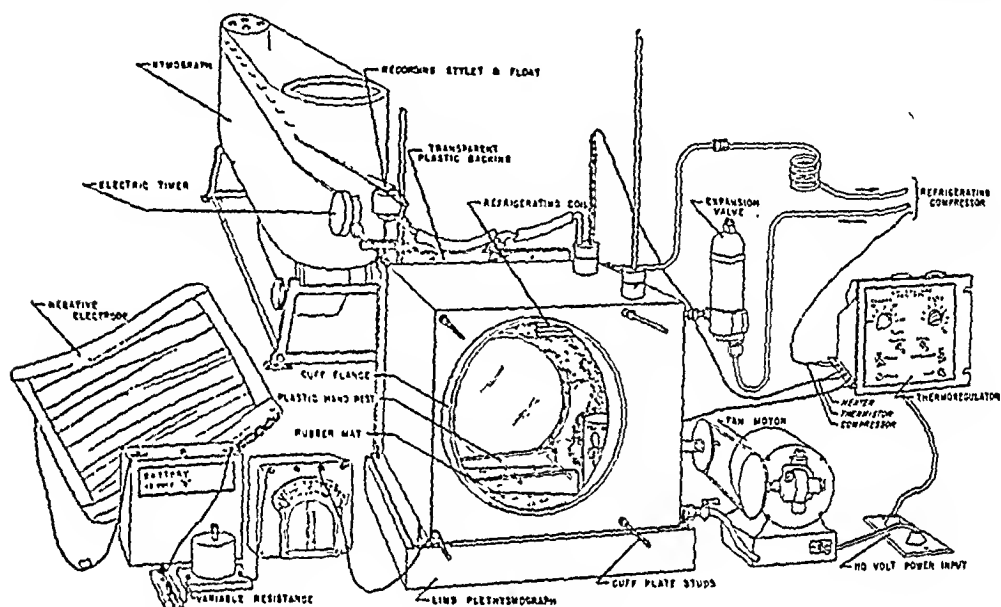


Fig. 1. VARIABLE TEMPERATURE PLETHYSMOGRAPH assembled for iontophoresis.

only twice. *Subject C*, who reacted most vigorously to ABMC, was studied on one occasion with a 0.4 per cent solution of ABMC. After 15 minutes of iontophoresis (18 milliamperes of current), he complained of dizziness, increased salivation and increased peristalsis. The experiment was terminated and the symptoms disappeared promptly after the administration of atropine. On another occasion, *subject F* complained of dizziness and abdominal cramps after a particularly prolonged period of iontophoresis. His face was flushed and perspiring profusely. The experiment was terminated and the signs and symptoms subsided rapidly.

Following ABMC iontophoresis, the hand remained flushed for several hours in every case where there had been an increase in blood flow. Visible and very marked sweating of the hand persisted for 3 to 12 hours after termination of the experiment. The sweating was confined to the dorsum of the hand and palmar sweating was never noted. The skin of the treated hand remained notably softer than that of the untreated hand for approxi-

mately 24 hours. Following one experimental period in which ABMC iontophoresis was continued for several hours, numerous petechiae appeared on the treated hand of *subject C*. These petechiae overlay the superficial veins for the most part. They were not associated with any discomfort and gradually faded after a few days.

### DISCUSSION

The actions of acetyl-choline and related compounds, originally investigated by Hunt and Taveau (16, 17), have excited the interest of physiologists since Dale (18) noted the remarkable manner in which acetylcholine duplicated the responses produced by stimulation of the parasymp-

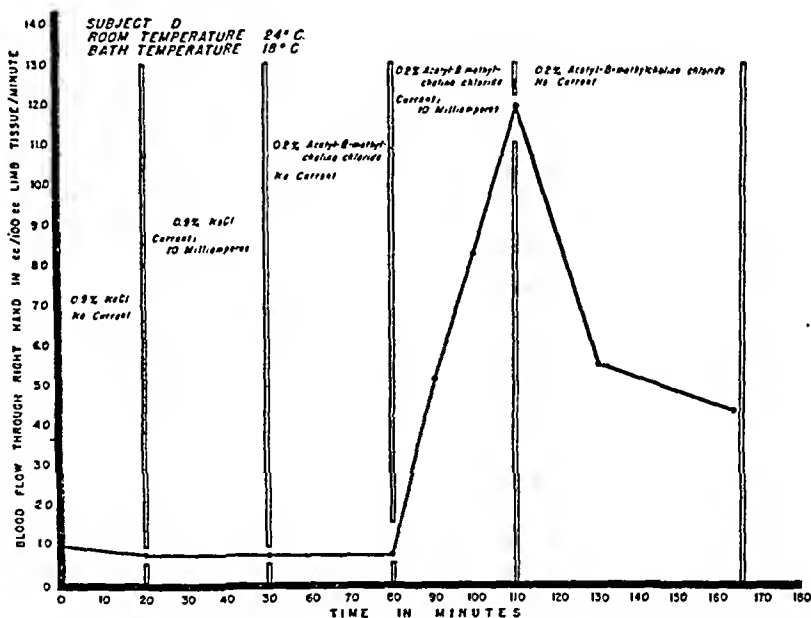


Fig. 2. EFFECT OF ACETYL-BETA-METHYLCHOLINE CHLORIDE IONTOPHORESIS on blood flow through the hand. Room temp. 24°C.; bath temp. 18°C.

pathetic nervous system, and Loewi (19) established proof that this substance is concerned in the mediation of nerve impulses. The preponderant experimental evidence indicates that ABMC and other autonomic drugs act directly on effector cells and not on nerve endings (6), although this concept has been challenged (20).

It is apparent from the results presented above that to a certain degree ABMC administered by iontophoresis is capable of overcoming locally the peripheral vasoconstriction produced by cold. Presumably such vasoconstriction is effected through sympathetic vasoconstrictor fibers and it is per-

haps significant that ABMC has been spoken of as "a physiological antagonist of epinephrine stimulating an opposing system of nerves" (2).

Abramson *et al.* (9) have shown that the effect of ABMC by iontophoresis is primarily upon cutaneous circulation and that the drug does not penetrate significantly into the muscle layers. This would explain the lack of maximal vasodilatation in the extremities following ABMC iontophoresis even within the temperature range at which the peripheral vascular bed is most labile. The wide variation in individual susceptibility to ABMC seen in these studies and also noted by previous investigators (4) is most probably due to variations in the amount of tissue cholinesterase present at any given time.

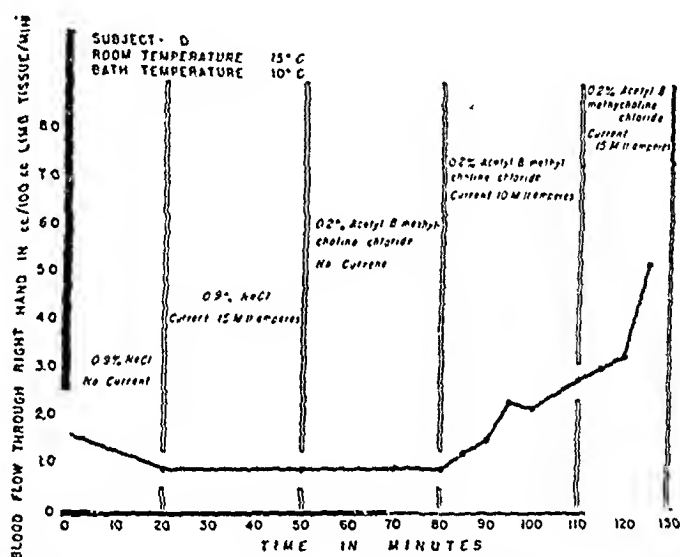


Fig. 3. EFFECT OF ACETYL-BETA-METHYLCHOLINE CHLORIDE IONTOPHORESIS on blood flow through the hand. Room temp. 15°C.; bath temp. 10°C.

In a study of patients with Raynaud's disease, Starr (2) found that oral administration of ABMC does not prevent the development of vascular spasm when the hands are exposed to severe cold, nor does it cause prompt relaxation of such spasm. It can, however, overcome or prevent spasm which follows more moderate exposure. Using larger doses of the drug in similar patients, Goldsmith (5) noted that the depression of hand skin temperature and the cyanosis following immersion of the hands in ice water was less marked if ABMC was administered several hours before immersion. Kovacs and his co-workers (4) have obtained striking relief of vasospasm in subjects with Raynaud's syndrome by ABMC iontophoresis. It is not altogether surprising, therefore, that direct measurements of peripheral blood flow in normal subjects should reveal an increase during ABMC iontophoresis at very low environmental temperatures.

From the present study it is not possible to determine whether, during exposure to severe cold, acetyl-choline is *a*) liberated in decreased amounts or entirely absent at the peripheral nerve endings or *b*) liberated in quantities approximating those at higher environmental temperatures but insufficient to overcome the increased vasoconstrictor tone mediated through sympathetic vasoconstrictor fibers. It should be possible to throw some light on this problem by utilizing one of the potent anti-cholinesterases, such as di-isopropyl fluorophosphate for iontophoresis at low temperatures.

The localization of the marked and persistent sweating response which almost invariably followed ABMC iontophoresis in our subjects is of considerable interest. Sweating, when it occurred, was always confined to the *dorsum* of the treated hand and never involved the palmar surface as far as could be discerned. The sweating response to ABMC has been studied by earlier workers (20, 21) and recently Randall (22) reported for the first time findings in reference to differences in palmar and dorsal hand sweating somewhat similar to those observed in these studies. In view of the fact that sweating in response to the emotional stresses of fear, anger or pain is confined primarily to the palms and involves the *dorsum* of the hand to little or no extent, while thermoregulatory sweating has precisely the opposite localization (23), these observations may be of significance. They suggest a difference in the functional innervation and/or a difference in a specific response of the effector organs of the two areas. It is, however, possible that ABMC is introduced by iontophoresis less readily through the palm than through the *dorsum* of the hand.

#### SUMMARY

Utilizing a specially constructed variable temperature plethysmograph, blood flow through the hand was studied in 6 normal subjects before and after iontophoresis of acetyl-beta-methyl-choline chloride. Under experimental conditions in which blood flow through the hand had been drastically curtailed by continuous exposure to cold, iontophoresis of ABMC usually resulted in a significant increase in hand blood flow. Although there were marked individual differences, 5 of the 6 subjects showed significant increases in blood flow through the treated hand, occasionally amounting to as much as 20 times the control flow. No indirect vasodilatation in the opposite hand, as estimated by changes in skin temperature, ever occurred. Iontophoresis of ABMC markedly diminished the pain or discomfort resulting from immersion of the hand in the bath at low temperatures. In the majority of cases the reaction to ABMC iontophoresis was confined to the treated hand. Mild systemic effects of the drug were observed only twice. Marked sweating of the hand persisted for 3 to 12 hours after ABMC iontophoresis. This

sweating was confined to the dorsum of the treated hand. Mere immersion of the hand in an ABMC bath without galvanic current had no effect on blood flow and no significant changes were noted when current was passed through the plethysmograph filled with normal saline. The possible significance of the vascular responses and the localized sweating resulting from ABMC iontophoresis have been discussed.

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## *Indirect Peripheral Vasodilatation Produced by the Warming of Various Body Areas<sup>1</sup>*

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**B**ECAUSE THE PERIPHERAL VASCULAR BED is of such major importance in the regulation of body temperature, numerous studies have been conducted in an effort to modify the conservation or dissipation of body heat by inducing vasoconstriction or vasodilatation in the extremities. The attainment of vasodilatation in the extremities is also a clinical desideratum in the treatment of certain peripheral vascular diseases and in the prevention of pathologic changes caused by cold-induced ischemia. Although particular emphasis has been directed toward the modification of peripheral blood flow by the direct application of thermal stimuli, various methods of inducing indirect<sup>2</sup> vasomotor changes have likewise received considerable attention. The ingestion of protein has been reported to cause an augmentation of peripheral blood flow (1) and recently it has been demonstrated that certain amino acids exert similar effects (2). Indirect vasodilatation and vasoconstriction produced by thermal stimuli have been studied in some detail (4-16).

German workers, engaged in military research during the recent war, obtained presumptive evidence (unpublished) that the face is a reflexogenous zone, the cooling of which induces marked vasoconstriction in the fingers. Although these investigators did not attempt to produce indirect vasodilatation, their work suggested that the face area might be a sensitive trigger zone for obtaining vascular responses of this nature.

During the course of experiments relating to the relative efficiency of various methods of rewarming men exposed to extreme cold, workers in our laboratory have demonstrated that infra-red warming of the face results in a significant rise in hand skin temperature, even though the latter be ex-

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<sup>2</sup> In the present paper, the terms 'indirect vasodilatation' and 'indirect vasoconstriction' refer to vascular changes produced by the introduction of various stimuli at some site or sites other than the vascular bed in which the changes occur.

tremely low initially (17). In view of these findings, and because of the physiological and clinical importance of devising satisfactory methods for producing indirect vasodilatation, the present study of peripheral vascular responses produced by warming various body surfaces was undertaken.

### METHODS

Measurements of skin temperatures, rectal temperatures and blood flow through the hands were made on two healthy, white, male subjects, aged 18 and 19 years. Forty experiments were carried out in a constant-temperature chamber with closed circuit ventilation and a turbulent air velocity of approximately three m.p.h. The studies were conducted at two ambient temperatures, 15°C. and 23.5°C. Room temperature was controlled to within  $\pm 0.5^\circ\text{C}$ . during any experiment.

Skin temperatures were obtained with No. 30 B and S copper-constantan thermocouples connected to a Leeds and Northrup potentiometer. The thermal junctions were secured to the skin with small pieces of light adhesive tape. On the left hand, 10 thermocouples were connected in parallel (with 6 on the hands and 4 on the fingers) so that one temperature reading gave an average value for the entire hand. Individual junctions were placed on the forehead, chest, right forearm, right thigh, left toe and infrascapular region. In those experiments where warming of the face was carried out (see below), 4 thermocouples connected in parallel (forehead, chin and both cheeks) were used to obtain an average face temperature. A similar arrangement was used to obtain average skin temperatures of the chest or foot and lower leg, when these areas were warmed. Rectal temperatures were measured by means of a thermocouple at the tip of a no. 14 soft rubber catheter inserted at least 8 cm. beyond the internal sphincter.

A hand plethysmocalorimeter (18) was used as an air plethysmograph, and blood flow records were obtained by the venous occlusion technique utilizing a modified Brodie bellows in the recording system. Each blood flow determination consisted of four to seven consecutive measurements taken at one-minute intervals; the average rate of flow was calculated in terms of cubic centimeters per 100 cubic centimeters of limb tissue per minute.

The subject, wearing a light cotton undershirt, light cotton shorts, fatigue trousers, light woolen socks and standard service shoes, entered the test chamber at 8 a.m. and remained at rest for approximately three to five hours. Throughout the test period all disturbing extraneous stimuli were avoided as far as possible. After skin and rectal thermocouples were secured, the subject was seated comfortably in an adjustable chair with the left hand in the plethysmograph approximately at heart level. Hand skin temperatures were followed until a steady state was reached, i.e., hand skin temperature varied no more than  $\pm 0.2^\circ\text{C}$ . for 40 minutes. When equilibrium had been reached, blood flow determinations were made.

Heat was then applied locally to the area selected for warming. The heat source was a screened 250-watt infra-red bulb, located at the base of an insulated double-walled metal cylinder (diameter 20 centimeters) and controlled by a rheostat. Adjustable wooden diaphragms were used over the open end of the apparatus to prevent leakage of heat when the cylinder was applied to the skin area. This instrument was used in warming the face and chest. A similar apparatus, consisting of an infra-red heating chamber, rheostatically controlled, was used for warming of the foot and lower leg. Heat was applied for a period of 90 minutes. The skin area being studied was kept at  $42^\circ$  to  $44^\circ\text{C}$ . throughout the warming period.

Hand skin temperature was determined at 10-minute intervals. Rectal temperatures and skin temperatures elsewhere were recorded every 20 minutes. Blood flow of the left hand was determined at the beginning and end of the warming period.

Control observations, without application of heat, were made at 23.5°C. ambient temperature. Subjective reactions were recorded in all the studies.

The surface area of each region heated was determined by covering the area with strips of vaseline-gauze, removing and photographing the strips, weighing the photographs and comparing them with a known standard.

### EXPERIMENTAL RESULTS

Surface areas of the various regions were determined on *subject P* and were found to be: face, 378 cm<sup>2</sup>; chest, 364 cm<sup>2</sup>; foot and lower leg, 1040 cm<sup>2</sup>. The results of experiments conducted at different ambient temperatures are considered separately.

#### *Studies at Environmental Temperature of 15°C.*

Twenty-four experiments on two subjects were conducted at an ambient temperature of 15°C. Each subject was used in six experiments in which the face was warmed, three experiments in which the chest was warmed and three experiments in which the left foot and lower leg were warmed. Skin temperature at which the hand reached equilibrium ( $\pm 0.2^\circ\text{C}$ . for 40 minutes) ranged between 16.0° and 20.0°C. By utilizing the rheostatic control, the average skin temperature of the area being warmed was quickly brought to 42° to 44°C., where it was maintained for the duration of the experiment.

In none of the chest-warming experiments did the hand skin temperature increase more than 0.9°C., and an average of the differences between the hand skin temperature before and after 90 minutes of heating the chest revealed an average *decrease* of 0.2°C. (table 1, fig. 1 and 2). Heating of the left foot and lower leg likewise resulted in little or no change in hand skin temperature (table 1, fig. 1 and 2).

In the 12 experiments in which the face was heated, the average rise in hand skin temperature after 80 minutes of face-warming was 9.8°C. The maximum rise obtained was 15.3°C. and the minimum rise was 3.5°C. (table 1). No significant changes in skin temperatures of the back, thigh or forearm occurred after warming of face, chest or leg, nor were any consistent alterations in rectal temperature noted. Heating the face resulted in a slight rise (average = 1.7°C.) in toe temperature of *subject C* after 80 minutes, but no rise in *subject P*. Neither chest-warming nor leg-warming produced any increase in toe temperature (table 1, fig. 3 and 4). The increases in hand skin temperature, when they occurred, generally appeared within 30 to 50 minutes.

Basal blood flow through the left hand ranged from 0.4 to 0.9 cc/100 cc. limb tissue/min. In the chest-warming experiments, the maximal increase



in blood flow through the hand was 0.3 cc/100 cc. limb tissue/min., with an average rise of 0.1 cc/100 cc. limb tissue/min. Similarly, warming of the left foot and lower leg resulted in no significant change in the blood flow through the hand (table 1). In sharp contrast to these results were the increases in hand blood flow which occurred in the face-warming experiments. Increases in blood flow through the hand amounting to as much as 6.8 cc/100 cc. limb tissue/min. were observed and the average rise was 3.1 cc/100 cc. limb tissue/min. (table 1).

*Studies at Environmental Temperature of 23.5°C.*

At an environmental temperature of 23.5°C., the equilibrium hand skin temperatures averaged 25.8°C. Six face-warming and six chest-warming

TABLE 1. SKIN TEMPERATURE, RECTAL TEMPERATURE AND PERIPHERAL BLOOD FLOWS AFTER HEATING VARIOUS SKIN AREAS

*Ambient temperature: 15°C.*

TIME OF WARM- ING	FACE HEATED TO 42-44°C.						CHEST HEATED TO 42-44°C. <sup>2</sup>						LEFT FOOT & LOWER LEG HEATED TO 42-44°C. <sup>3</sup>						
	Blood flow left hand		Temperature, °C.				Blood flow left hand		Temperature, °C.				Blood flow rt. hand		Temperature, °C.				
			Hand <sup>1</sup>	Toe <sup>2</sup>	Rectal <sup>1</sup>	Hand			Toe	Rectal	Hand	Toe			Rectal				

*Subject P*

min.													
0	0.6	17.8	17.2	37.2	0.4	17.9	16.6	37.0	0.3	18.4			36.9
10		17.7				17.7				18.0			
20		18.5	17.0	37.2		17.8	16.4	37.1		17.9			37.0
30		19.3				17.8				17.7			
40		20.5	16.8	37.2		17.9	16.5	37.1		17.6			36.9
50		22.1				18.1				17.4			
60		23.6	16.5	37.4		18.0	16.5	37.1		17.4			36.9
70		24.5				17.9				17.4			
80		26.4	16.4	37.4		17.8	16.2	37.2		17.3			37.0
90	3.7	26.1			0.4	17.9			0.4	17.3			

*Subject C*

0	0.4	17.8	15.8	37.3	0.3	18.1	15.4	37.2	0.3	17.4	16.3		36.9
10		18.2				18.1				17.3			
20		18.9	15.6	37.4		18.0	15.2	37.4		17.1	16.3		36.9
30		21.5				17.9				17.0			
40		24.2	16.6	37.4		17.9	15.2	37.3		16.8	16.2		36.9
50		25.5				17.9				16.6			
60		26.8	17.4	37.4		18.1	15.0	37.3		16.3	16.2		36.8
70		28.1				18.0				16.3			
80		28.8	17.5	37.4		17.7	15.1	37.3		16.3	16.2		36.8
90	3.5	27.0			0.4	17.8			0.3	16.1			

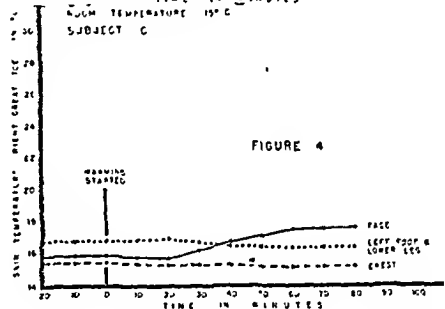
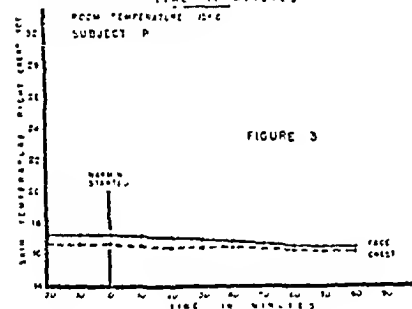
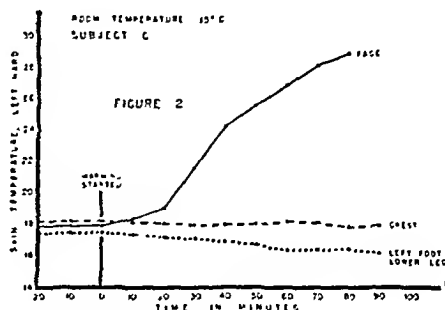
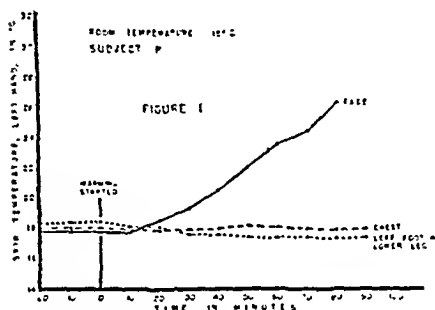
Blood flow of hand in cc/100 cc. of limb tissue/min.

<sup>1</sup> Average of 6 experiments.

<sup>2</sup> Average of 5 experiments.

<sup>3</sup> Average of 3 experiments.

experiments were conducted on two subjects. At this ambient temperature, warming of *either* the face or the chest resulted in significant increases in skin temperature and blood flow of the hand. In almost every case the hand temperature began to rise within 10 minutes after warming of the selected skin area was instituted (table 2, fig. 5 and 6). Face-warming resulted in an average hand skin temperature increase of  $9.3^{\circ}\text{C}$ . ( $8.4^{\circ}\text{C}$ . in



Figs. 1 and 2. AVERAGE SKIN TEMPERATURE, left hand, after warming various body areas to  $42-44^{\circ}\text{C}$ .

Figs. 3 and 4. AVERAGE SKIN TEMPERATURE, right great toe, after warming various body areas to  $42-44^{\circ}\text{C}$ .

the case of *subject P* and  $10.2^{\circ}\text{C}$ . in the case of *subject C*). Chest-warming produced an average hand skin temperature increase of  $7.5^{\circ}\text{C}$ . ( $8.1^{\circ}\text{C}$ . in *subject P* and  $6.9^{\circ}\text{C}$ . in *subject C*).

Significant rises in toe temperature were observed when either the face or the chest was warmed. Toe temperature increases averaged  $6.3^{\circ}\text{C}$ . in the face-warming series and  $5.6^{\circ}\text{C}$ . in the chest-warming series (table 2, fig. 7 and 8). No consistent changes in rectal temperature or skin temperature elsewhere were noted in any of the warming experiments conducted at this room temperature.

Blood flow measurements paralleled the observations on hand skin temperature. Basal blood flow through the hand averaged  $1.0\text{ cc}/100\text{ cc}$ . limb tissue/min. Chest-warming resulted in an average increase of  $3.8$

cc/100 cc. limb tissue/min. and face-warming resulted in an average of 6.0 cc/100 cc. limb tissue/min. (table 2).

Control studies, in which skin temperatures and blood flow were determined for a similar time period after equilibrium had been reached but in which no skin area was warmed, revealed no significant changes in toe temperature, hand skin temperature or blood flow through the hand (table 2).

#### DISCUSSION

Early investigators of indirect peripheral vascular responses to thermal stimuli generally agreed that these vasomotor changes were mediated via a reflex arc which had its origin in cutaneous thermoreceptors. Brown-Sequard and Tholozan (4, 5), Francois-Franck (6) and Fredericq (8) observed that cold stimuli applied to one limb rapidly effected vasoconstrictive changes in the contralateral extremity. Winkler (7) in 1902 noted that the flushing of the ears which normally occurs when a rabbit's hindquarters are immersed in warm water is markedly delayed after spinal cord transection, and he concluded that reflexes arising in the skin account for indirect vasodilatation as well as indirect vasoconstriction. More recently, however, it has been shown (19) that indirect vasodilatation of the rabbit ear is not a specific response to heat but may be produced if the opposite ear is immersed in ice water.

It remained for Pickering (11) and Gibbon and Landis (12), some 30 years later, to elucidate more fully the nature of indirect vasomotor responses. Pickering observed that the application of cold to the skin of an extremity whose venous return had been occluded by a tourniquet produced transient vasoconstriction in the other extremities. The vasoconstriction thus produced could be quickly abolished by again warming the skin of the stimulated extremity. Releasing the tourniquet resulted in additional indirect vasoconstrictive changes which could not be abolished rapidly by warming elsewhere. In contrast to these findings relating to indirect vasoconstriction, Pickering reported that indirect vasodilatation was not produced by hot-water immersion of an extremity if the venous return from that extremity was occluded. Marked indirect vasodilatation occurred, however, if the circulation of the immersed limb was not arrested. He concluded that indirect vasoconstriction is due in part to reflexes arising in cutaneous thermoreceptors and in part to the action of a central mechanism excited by cool blood returning from the skin. He attributed indirect vasodilatation solely to the action of a central mechanism excited by a rise of blood temperature. Gibbon and Landis, on the basis of similar experimental findings, also reported that indirect vasodilation depends upon the

return of warmed blood from the immersed extremity (12). Freeman (16) confirmed these observations in part and reported that application of cold to the chest caused a decrease in the blood flow through the sympathectomized hand. He considered the decrease to be the result of circulating epinephrine.

TABLE 2. SKIN TEMPERATURE, RECTAL TEMPERATURE AND PERIPHERAL BLOOD FLOWS AFTER HEATING VARIOUS SKIN AREAS

*Ambient temperature: 23.5°C.*

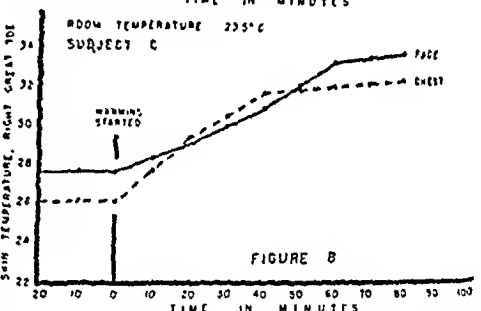
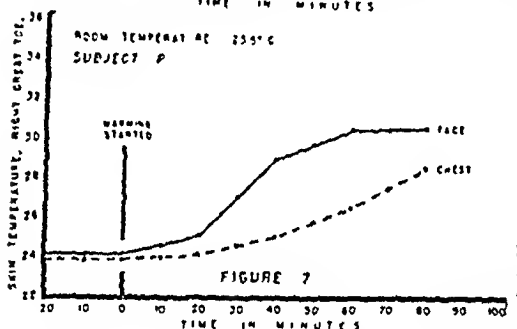
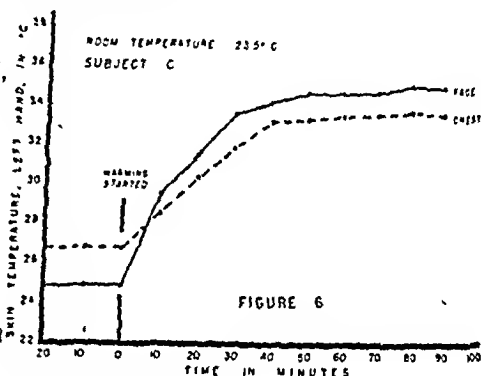
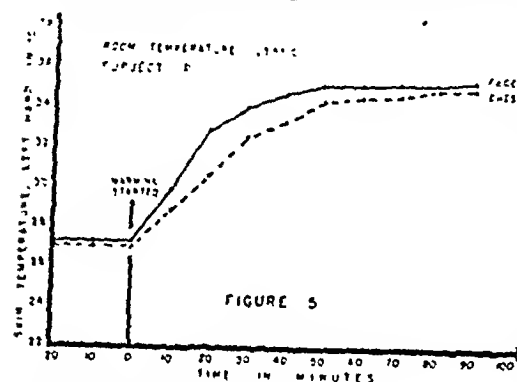
TIME OF WARM- ING	FACE HEATED TO 42-44°C. <sup>1</sup>				CHEST HEATED TO 42-44°C. <sup>1</sup>				CONTROLS <sup>2</sup>			
	Blood flow left hand	Temperature, °C.			Blood flow left hand	Temperature, °C.			Blood flow left hand	Temperature, °C.		
		Hand <sup>1</sup>	Toe <sup>1</sup>	Rectal <sup>1</sup>		Hand	Toe	Rectal		Hand	Toe	Rectal
Subject P												
min.												
0	1.5	27.2	24.1	37.1	1.2	27.1	23.9	37.5	0.6	24.4	23.5	37.1
10		29.9				28.9				24.5		
20		32.9	25.0	37.1		30.6	24.1	37.4		24.4	23.4	37.1
30		34.1				32.6				24.5		
40		34.8	29.0	37.0		33.4	25.0	37.4		24.4	23.0	37.0
50		35.3				34.5				24.5		
60		35.2	30.5	37.0		34.7	26.5	37.4		25.2	22.9	37.0
70		35.4				34.8				25.1		
80		35.4	30.6	36.9		35.4	28.6	37.4		25.0	22.9	37.1
90	9.2	35.6			6.1	35.2			0.8	25.0		
Subject C												
0	0.7	24.8	27.6	37.2	1.2	26.7	26.1	37.3	0.8	25.2	27.6	37.2
10		29.4				28.5				25.4		
20		31.6	29.1	37.1		30.3	29.3	37.2		25.3	27.8	37.2
30		33.5				31.8				25.0		
40		34.1	30.9	36.9		33.2	31.7	37.1		24.9	27.5	37.3
50		34.6				33.6				24.9		
60		34.6	33.3	37.0		33.5	32.1	37.2		24.9	27.4	37.5
70		34.7				33.6				24.8		
80		35.1	33.7	36.9		33.8	32.4	37.2		24.8	27.6	37.5
90	5.0	35.0			3.8	33.7			0.5	24.6		

Blood flow values are cc/100 cc. limb tissue/min.

<sup>1</sup> Average of 3 experiments.    <sup>2</sup> Average of 2 experiments.

The fact that localized warming or cooling of the brainstem in the region of the hypothalamus results in peripheral vasodilatation or vasoconstriction has been demonstrated repeatedly by numerous investigators (20-24) and the importance of this area for the regulation of body temperature is too well known to require discussion here.

Relatively little has been done in the past to determine the comparative effectiveness of heating various body areas as a means of inducing indirect vasodilatation. It has been noted that altering the temperature of the stomach by irrigation with cold or hot water results in vasoconstriction or vasodilatation in the extremities (11, 25, 26). In 1945, Martinez and Visscher (14) reported that "local heating by immersion in water at 43° to 44°C. produces a larger rise in skin temperature in all locations except the



Figs. 5 and 6. AVERAGE SKIN TEMPERATURE, left hand, after warming various body areas to 42-44°C.

Figs. 7 and 8. AVERAGE SKIN TEMPERATURE, right great toe, after warming various body areas to 42-44°C.

back when the two forearms are immersed than when the legs, up to the knee, are immersed". They found this to be the case even though the latter skin area was greater than the former. Martinez and Visscher felt that the variation in blood flow through the two areas (27) probably accounted for the difference.

It is evident from the experimental results set forth in the preceding section that the present study has demonstrated significant differences in the effectiveness of warming various skin areas as a means of inducing indirect vasodilatation in the extremities. These differences are most marked in the subject exposed to a low ambient temperature for a period sufficiently long to allow the peripheral vascular bed to reach a relatively steady state. Under these circumstances, the cold acts as a potent stimulus for generalized peripheral vasoconstriction and, as has been shown in other studies

from this laboratory (3, 15, 28), the tone of the peripheral vessels is much less labile than at high environmental temperatures.

At an ambient temperature of  $15^{\circ}\text{C}.$ , the increases in skin temperature and blood flow of the extremities induced by warming the face were strikingly greater than those induced by heating an approximately equal area of the chest or a much greater surface area of one lower extremity. The differences in the results obtained at an environmental temperature of  $15^{\circ}\text{C}.$  and those obtained at an environmental temperature of  $23.5^{\circ}\text{C}.$  are in agreement with the findings of Ferris *et al.* (15). These investigators demonstrated that under cold ambient conditions ( $18^{\circ}\text{C}.$ ) it is extremely difficult to induce vasodilatation, but at an ambient temperature of  $24^{\circ}\text{C}.$  the introduction of a relatively small amount of heat is sufficient to elicit indirectly a marked increase in blood flow through the hand.

It is of considerable interest that the only sites at which skin temperature rises occurred were the hands and the toes. The vascular anatomy of these two areas differs from the peripheral vascular bed elsewhere in that arteriovenous shunts are present in the toes, fingers, thenar and hypothenar eminences (30). Differences between the physiological reactions of blood vessels at these sites and the peripheral vascular bed in other portions of the body have been demonstrated by numerous investigators (3, 30, 31, 32).

It cannot be concluded definitely, on the basis of these experiments, that the changes observed were mediated through a reflex arc originating in cutaneous thermoreceptors or that they represent a purely central phenomenon due to the excitation by warmed blood of a heat-sensitive area of the central nervous system. The latter view is supported by the length of time which elapsed before the skin temperature of the extremities began to rise. In no instance did the stimulus-response relationship demonstrate the rapidity characteristic of a reflex change and we do not believe that the 'trigeminal reflex' described by Ebbecke (33, 34) is concerned with these phenomena. On the other hand, it must be emphasized that skin temperature in these studies represented a variable which was dependent upon blood flow. Since blood flow measurements were made only at the beginning and end of each experiment, it is not possible to state how quickly the augmentation of flow occurred. The richly abundant vascular supply of the face may be of more importance than any specialized heat-sensitive receptors peculiar to this area. The warming of the inspired air during the face-warming experiments may also have played a significant rôle, although we have estimated that not more than five large cal./hr. were contributed to the body in this manner.

The nature of the efferent pathway of the vasodilatation response is not clear. Sympathetic vasodilator fibers have been described (13, 35, 36) but

whether peripheral vasodilatation is effected through these nerves or occurs simply as a result of inhibition of vasoconstrictor tone is debatable. Although Barcroft, Bonnar and Edholm (37), have recently presented additional evidence to suggest that reflex vasodilatation to heat is mediated by sympathetic fibers, the functional significance (38), distribution and, indeed, the very existence (39) of vasodilator fibers have been questioned. On the basis of available evidence, it seems reasonable to assume that indirect vasoconstriction in man is due in part to sensory impulses from the stimulated area and in part to the cooled blood returning from the stimulated portion of the body. Indirect vasodilatation, on the other hand, is probably due entirely to the heat carried into the body by the venous blood returning from the warmed area.

It is extremely difficult to maintain an adequate flow of blood through the extremities of men exposed to severely cold environments. The results of the present study suggest that the maintenance of a high skin temperature of the face area (perhaps by means of a face mask) may be of considerable importance in preventing the pathologic changes in the extremities caused by cold-induced ischemia.

#### SUMMARY

1. Skin temperatures, rectal temperature and blood flow through the left hand were studied in two healthy young males before and after infra-red heating of various skin area to  $42^{\circ}$  to  $44^{\circ}\text{C}$ . Heat was applied for 80 to 90 minutes after a steady state had been attained. The regions heated were the face, chest, left foot and lower leg. The surface areas, as determined for one subject, were  $378\text{ cm}^2$ ,  $364\text{ cm}^2$ , and  $1040\text{ cm}^2$  respectively.

2. At an ambient temperature of  $15^{\circ}\text{C}$ ., face-warming resulted in a significant rise in skin temperature of the left hand. The average rise was  $9.8^{\circ}\text{C}$ ., the maximum increase being  $15.3^{\circ}\text{C}$ . and the minimum increase being  $3.5^{\circ}\text{C}$ . Face-warming at this ambient temperature caused a slight rise in the toe temperature of one subject and no change in the toe temperature of the other subject.

3. At an ambient temperature of  $15^{\circ}\text{C}$ ., face-warming produced a significant increase in blood flow through the hand, as measured by venous occlusion plethysmography. The average increase in blood flow through the left hand was  $3.1\text{ cc}/100\text{ cc. limb tissue}/\text{min}$ .

4. At an ambient temperature of  $15^{\circ}\text{C}$ ., warming of either the chest or of one lower extremity from the toes to just below the knee caused no significant changes in skin temperature or peripheral blood flow.

5. At an ambient temperature of  $23.5^{\circ}\text{C}$ ., warming either the chest or the face to  $42^{\circ}$  to  $44^{\circ}\text{C}$ . for 90 minutes resulted in significant rises in skin

temperature of the hands and toes. Face-warming resulted in an average hand skin temperature increase of  $9.3^{\circ}\text{C}.$ , and an average rise of  $6.3^{\circ}\text{C}.$  in toe temperature. Chest-warming resulted in an average hand skin temperature increase of  $7.5^{\circ}\text{C}.$  and an average rise of  $5.6^{\circ}\text{C}.$  in toe temperature.

6. At an ambient temperature of  $23.5^{\circ}\text{C}.$ , both face-warming and chest-warming produced an augmentation of blood flow through the left hand. Face-warming was followed by an average increase in flow of 6.0 cc/100 cc. limb tissue/min. Chest-warming elicited an increase of 3.8 cc/100 cc. limb tissue/min.

7. No consistent alterations in rectal temperature or skin temperature of back, forearm or thigh were noted in any of the warming experiments.

8. Significant differences in the effectiveness of warming various skin areas as a means of inducing indirect vasodilatation in the extremities have been demonstrated. The experimental results suggest that maintaining a high skin temperature of the face may be of value in the prevention of pathologic changes in the extremities caused by cold-induced ischemia.

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## *Variation of Total Circulating Hemoglobin and Reticulocyte Count of Man with Season and Following Hemorrhage*

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IT IS NOW WELL ESTABLISHED that change in environmental temperature alters blood volume (1-5). During periods of a few days of exposure to heat, blood volume increases at first by simple dilution and later by increase in the amount of circulating plasma protein. As a result, hemoglobin concentration declines by 5 to 10 per cent below values obtained at comfortable temperatures. There may also be an increase in quantity of circulating hemoglobin. However, this increase must be considerably less than reported originally by Barcroft (3), since recent investigators have found total circulating hemoglobin to change only slightly (4) or to remain constant in such experiments (1, 2). Opposite effects follow exposure to cold.

The influence of season on blood volume has been studied less thoroughly. As a result of seasonal changes in environmental temperature, one might expect that blood volume and hemoglobin concentration would change as in the experiments cited above. The fact that a significant seasonal variation in normal hemoglobin concentrations has not been found clinically is presumptive evidence that hemoglobin concentration remains essentially constant throughout the year. Presumably the changes observed in the short-term experiments cited above must be sufficiently transient under ordinary circumstances to have escaped the attention of clinicians, and one might conclude either that blood volume is influenced only temporarily by changes in environmental temperature or that the amount of circulating hemoglobin alters to correspond with the change in blood volume. The most extensive studies on quantity of circulating hemoglobin at different seasons of the year (4, 5) favor the latter view, as do the observations of Friedlander and Wiedimer (6) and of Grunke and Diesing (7) that a moderate reticulocytosis (indicating an increased rate of hemoglobin formation) occurs at the onset of the warm season. The present report describes observations extending over a period of more than a year on both quantity of circulating hemoglobin and reticulocyte count. Also included in this report

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are data obtained following venesection (500 cc.) performed to test the adequacy of our methods.

### METHODS

Total hemoglobin was determined by measuring blood carboxy-hemoglobin concentrations before and after administering a known quantity of carbon monoxide. The procedure and electric photometer previously described were used (2, 5). Hemoglobin concentrations were measured on the photometer. Plasma protein concentrations were determined by specific gravity (8). The ratio of total circulating hemoglobin to total plasma protein,  $R$ , was calculated from the following formula:

$$R = \frac{\text{Hemoglobin concentration}}{\text{Protein concentration (1 - hematocrit)}}$$

Reticulocytes were counted at first by the stained dry smear method and later by the oxalated wet film method (9). No consistent difference was found between the results of the two methods in ten sets of paired determinations. Each count, of 5000 cells, was made by a single observer and will be expressed as reticulocytes per 1000 red blood cells. Five counts at two-hour intervals on a single day on one subject showed no trend and gave a mean value of 6.5 (standard deviation =  $\pm 1.4$ ). The probability of getting a greater variation from the average by random sampling is 9.8 per cent by the chi square test.

### DESCRIPTION OF EXPERIMENTS

*Seasonal Study.* Total hemoglobin and reticulocyte count were determined on four young men<sup>2</sup> at about two-week intervals. Total hemoglobin was measured between May 1946 and September 1947; reticulocyte counts were made from November 1946 to August 1947. Two of the men,  $R$  and  $Y$ , were subjects of previously reported experiments (2) in which they were kept uncomfortably cold for six days in July and uncomfortably warm for six days in December 1946. However, no consistent change in quantity of hemoglobin or reticulocyte count (see below) was observed at these times. These subjects,  $R$  and  $Y$ , were not observed in July and August 1947. Subject  $P$  was not observed in the summer of 1946.

*Hemorrhage Experiment.* Eight to 12 per cent of the total hemoglobin of 4 other healthy young men<sup>3</sup>, as measured by the mean of two determinations, was removed by venesection. Blood samples were drawn 12 hours later and subsequently at intervals of one to four days for a month. Plasma protein, hemoglobin concentration and hematocrit were determined on all four men but total hemoglobin was determined on only one man at a time in rotation. Reticulocytes were counted almost every day for 4 days before and 15 days after bleeding.

### RESULTS AND DISCUSSION

*Seasonal Study.* Total circulating hemoglobin (fig. 1) showed no significant variation with season except an increase of 40, 50 and 100 grams for subjects  $R$ ,  $S$ , and  $Y$ , respectively, in the summer of 1946. This increase is

<sup>2</sup>  $P$ : age 26; ht. 174 cm.; wt. 67 kgm.  $R$ : age 23; ht. 178 cm.; wt. 59 kgm.  $S$ : age 38; ht. 172 cm.; wt. 62 kgm.  $Y$ : age 21; ht. 160 cm.; wt. 51 kgm.  
<sup>3</sup> Range in age, 23 to 26; in ht., 165 to 180 cm.; in wt., 57 to 78 kgm.

a change of 6 to 11 per cent in the total quantity. There was no such increase in the summer of 1947 except a single elevated value for *subject R* in June 1947. No satisfactory explanation has been found for the difference in amount of total hemoglobin found in the summer of 1946 as compared with the summer of 1947. The two years were very similar as regards outdoor temperature (fig. 4). The outstanding differences are that warm weather began a month earlier in 1946 than in 1947 and that the summer of

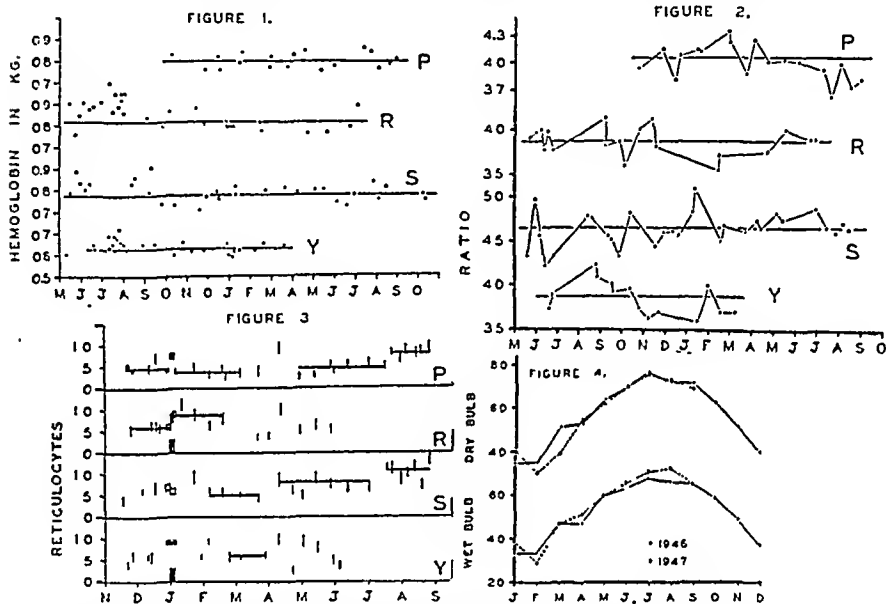


Fig. 1. TOTAL HEMOGLOBIN IN KGm. of 4 men (*P*, *R*, *S* and *Y*) determined by carbon monoxide during the years of 1946 and 1947. The heavy straight lines represent the approximate hemoglobin levels existing from October through May.

Fig. 2. RATIO OF TOTAL CIRCULATING HEMOGLOBIN to total plasma protein during the years 1946 and 1947, as determined from the formula  $\frac{\text{Hb. conc.}}{\text{Pr. conc. (1-hematocrit)}}$

Fig. 3. RETICULOCYTES PER 1000 RED BLOOD CELLS in 4 men during 1946 to 1947. Averaged counts are plotted as  $\pm$  one standard deviation and are shown as hollow blocks if they extend over several days. For single counts the formula  $\sigma = \sqrt{n p q}$  is used. Mean values of more than 5 counts, whose components deviate no more than randomly, ( $P > 10$  per cent) are indicated by horizontal lines. Significant differences exist between all adjacent means ( $P < 1$  per cent) except for the difference between March and May in *subject P*. The time of experimental exposure to heat is indicated by the solid blocks.

Fig. 4. CLIMATIC DATA FOR 1946 to 1947. Outdoor dry bulb temperatures in degrees Fahrenheit are monthly means of mean daily temperature at the City Office of the Weather Bureau in Philadelphia. Wet bulb temperatures are monthly means of values taken daily at 1:30 p.m. at the Southwest Airport of Philadelphia.

1947 was more humid than that of 1946. The increase in total hemoglobin found in the summer of 1946 was of the same magnitude as that observed by Maxfield *et al.* (5).

The ratio of total circulating hemoglobin to total circulating plasma protein (fig. 2) demonstrates no consistent trend with season such as might be expected in the presence of changes in total quantity of plasma protein without changes in total hemoglobin. Results obtained during the experiments mentioned above (2) are not included. Hemoglobin and protein concentrations are not presented separately since blood samples were not taken under controlled conditions.

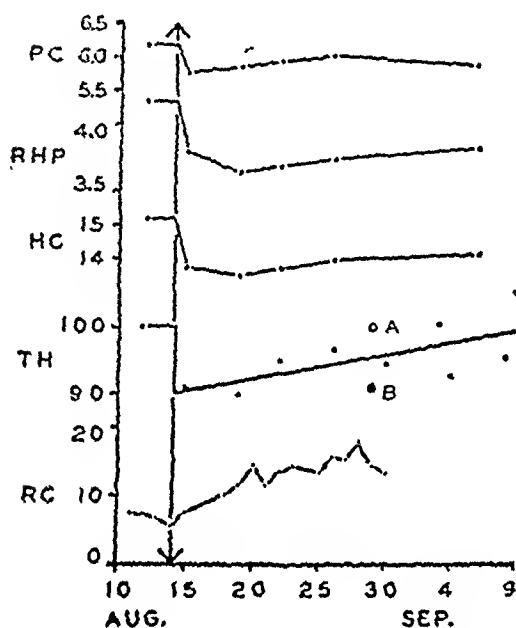


Fig. 5. TOTAL HEMOGLOBIN in percentage of normal (TH), hemoglobin concentration in grams per cent (HC), protein concentration in grams per cent (PC), ratio of total hemoglobin to total plasma protein (RHP) and reticulocyte count per 1000 red cells (RC) before and after 500 cc. hemorrhage indicated by arrow. Except for total hemoglobin (see text) values are means of 4 subjects. A and B refer to theoretical points mentioned in the text.

Reticulocyte counts are shown in figure 3. *Subjects R and Y* both showed temporary elevations of count during experimental exposure to heat in December-January 1946-1947 mentioned above (2). However, in *Y* a significant elevation was observed during the three days before exposure. There was no indication whether the persistence of this elevation during the exposure to heat was related to this exposure or not. Also, one of the subjects, *P*, who was an observer in these experiments but was little exposed to heat, showed a brief elevation. On April 10 to 11, four to five days after a very hot day (24° F. above normal), all 4 subjects showed a marked elevation in count, but this state persisted in only one of them, *S*. In July 1947 *P* and *S*, the only remaining subjects, showed an average elevation from a count of 5.8 to a count of 9.4. Thus the reticulocyte counts do not show an entirely consistent relationship to environmental temperature. Although persistent increases were noted in the heat of summer and a temporary one following a very warm day in the spring, the response to the experimental heat to which two of the subjects were exposed in the winter was not clearly related to this exposure, nor was there any unseasonably hot weather to account for a premature rise in the reticulocyte count.

Perhaps the most important conclusion that can be made from our study is that large seasonal variations did not occur. Values for total circulating hemoglobin during the summer of 1946 and reticulocyte counts obtained in the summer of 1947 indicate that hemoglobin may increase slightly in warm weather, but the changes were so small as to be difficult to demonstrate with our techniques. It seems probable that some subjects exhibit greater changes (for example, *subject R* of our experiments) than do others, and this fact may account in part for some of the larger seasonal fluctuations that have been reported. It also seems likely that more pronounced effects would be observed if artificial means for maintaining thermal comfort throughout the year were not so readily available.

*Hemorrhage Experiment.* The total hemoglobin, and mean hemoglobin concentration, mean plasma protein concentration, mean ratio of total hemoglobin to total protein and mean reticulocyte count are shown in figure 5. The fall in total hemoglobin (about 10 per cent) was as large as was expected from the quantity removed by bleeding (8 to 12 per cent). Two weeks after hemorrhage  $6 \pm 4$  per cent of the original amount had been regenerated as indicated by inspection of figure 5. Regeneration appeared to be almost complete at the end of one month. Protein and hemoglobin concentrations and ratio decreased following hemorrhage. Protein concentration subsequently approached normal more rapidly than did the ratio, while hemoglobin concentration increased still more slowly and was 6 per cent below the original level at the end of the month. The mean reticulocyte count rose from a control value of 6.7 to a peak of 18.0 14 days after hemorrhage. The mean of all counts for this 14-day period was 12.6. One of the subjects consistently showed a lower count than the other three by about four, but his total hemoglobin and hemoglobin concentration were normal. The reticulocyte response was distinct and the peak occurred later (18th day) than is found clinically after hemorrhage (4th to 7th day, 9). One other similar hemorrhage experiment that we performed on a normal man showed a rise to only 11.9 from 7.4 which lasted from the 5th to 9th day.

Fowler and Barer (10), who may be consulted for other references, followed hemoglobin regeneration after hemorrhage (500 to 600 cc.) using only hemoglobin concentration as an index of recovery. Calculations on their data show an average degree of regeneration similar to ours (5.4 per cent) at the end of two weeks, but their average total recovery time (50 days) was longer than ours. Their recovery times showed a great range of normal variation, however. It may be noted that total hemoglobin returned to normal more rapidly than hemoglobin concentration in our experiment. This fact suggests the possibility that blood volume may become larger than normal for a time following hemorrhage.

*Comment on the Relationship between Reticulocytosis and Hemoglobin Re-*

*generation.* The relationship between reticulocyte count and hemoglobin formation after hemorrhage is not well defined. Schiødt suggested that the rate of blood formation remains unchanged and that the rise in total hemoglobin is due to proportionately decreased destruction of red cells (11). If

this is the case and the life of the red cell is 120 days (12), then  $\frac{0.1 \times 14}{120}$  or

1.2 per cent of the original amount of hemoglobin should have been regained in the 14 days during which observations were made. This amount, plotted on figure 5 as theoretical point *B*, lies at the lower limit of the range of hemoglobin regeneration which we observed. Another reasonable assumption would be that hemoglobin formation is proportional to reticulocyte count.

Calculations on this basis with destruction as above show that  $\frac{12.6 \times 14}{6.7 \times 120} -$

$\frac{0.9 \times 14}{120}$ , or 11.4 per cent of the original amount of hemoglobin, should

have been reformed at the end of 14 days. This point, *A* in figure 5, is at the upper limit of the amount of hemoglobin which we observed to be regenerated in this time. Neither of these two theories is in accord with our results. Accepting the more probable view that increased red cell production is associated with increased reticulocyte count, one must conclude either that the reticulocytes mature more slowly or that a greater proportion of cells leave the marrow in the reticulocyte stage of development after hemorrhage than normally.

#### SUMMARY

1. The total circulating hemoglobin determined by carbon monoxide in 4 men remained approximately constant from October 1946 to May 1947. Most of the values were within a range of  $\pm 5$  per cent of the mean. In the summer of 1946 there was an increase of 6 to 11 per cent but a comparable increase was not observed in the summer of 1947. Reticulocyte counts showed a slight temporary rise during experimental exposure to heat in December 1946, following a day of hot weather in April 1947, and also a rise in continued hot weather in July 1947. These elevations in reticulocyte count could not be attributed with certainty to the changes in temperature. These changes in count are slightly smaller than those previously reported as taking place in the spring.

2. Total circulating hemoglobin regeneration following 500 cc. hemorrhage was almost complete after four weeks but hemoglobin concentration was still low. The reticulocyte count rose from a normal of 6.7 to a peak of 18 per thousand red cells on the 14th day.

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## *Regional Differences in the Basal and Maximal Rates of Blood Flow in the Skin*

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THE MEAN CUTANEOUS BLOOD FLOW has been estimated to be less than 0.015 cc/cm<sup>2</sup>/min. in the normal nude subject in the basal state and in an environmental temperature of less than 28°C. (1). An average value of 0.005 cc/cm<sup>2</sup>/min. (range: 0.0008-0.016) was obtained at a room temperature of 25°C. (2). As the room temperature rose above 28°C. the estimated skin blood flow increased linearly with the rise in temperature. These estimates were calculated from data on heat production, heat loss, skin temperatures, rectal temperatures and estimates of the thermal conductivity of the superficial tissues and the thermal gradients therein. They agree quite well with independent estimates of skin flow from the cutaneous uptake of helium (3), although the latter values appear to be somewhat higher.

The thermal and the helium uptake methods aim to measure the *total* cutaneous blood flow. The relative contributions to the total flow which are made in the various skin areas of the head, trunk, arm, legs, hands and feet are not indicated in the published data on total flow. At first glance, the thermal method would seem to offer an opportunity to calculate these various contributions, since the equation for estimating skin flow contains a quantity, the mean skin temperature, which is equal to the sum of the products, skin temperature times weighted skin area, in the various skin areas. However, in order to fractionate the total cutaneous blood flow by thermal methods it is also necessary to measure the heat loss and the heat storage in each part of the body. Even a casual inspection of published data on cutaneous blood flows and temperatures in the finger and forearm indicates that the rate of blood flow in each cutaneous area is not necessarily indicated by the skin temperature. The qualitative correlation between skin temperature and blood flows is useful, but the quantitative relations are complex. Our own experience indicates that if one attempts to estimate the blood flow in a particular cutaneous area by currently available thermal methods during a period of changing flow, the data at best will provide only qualitative information and in some circumstances may indicate incorrectly the direction of the changes.

The possibility of estimating regional differences in the rate of blood flow in the skin by means of photoelectric recordings of the skin pulses was recognized early in the devel-

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opment of the photoelectric plethysmograph (4). Its recent calibration (5) now offers an opportunity to measure the blood flows in the various skin areas of the body. The sum of these flows should equal the total cutaneous blood flow. If the measurements are made on normal subjects in a basal state and under environmental conditions which are comparable to those provided when the total cutaneous blood flow was estimated from thermal data (2), the photoelectric estimates of the total cutaneous blood flow should approximate the thermal estimates.

The experimental demonstration of this agreement would emphasize the essential correctness and dependability of the photoelectric criteria of cutaneous blood flow. The validity of these data in turn would permit an examination of the vascular adjustments which are made in the various skin areas and of the mechanisms of these adjustments.

#### TOTAL CUTANEOUS BLOOD FLOW UNDER BASAL CONDITIONS

The basal blood flows in the various skin areas of the body were estimated from the consecutive recordings of the corresponding cutaneous volume pulses by the photoelectric plethysmograph. The blood flow in the individual skin area is obtained from the product  $K_f \cdot P \cdot A$ , where  $A$  is the area of the skin exhibiting volume pulses of approximately equal amplitudes,  $P$  is the average amplitude of the photoelectrically recorded skin pulses, and  $K_f$  is the flow equivalent of the skin pulse.

Usually, 30 to 40 recordings were taken during a period of 90 minutes. Repeated experiences in sampling the skin pulses indicated that the choices expressed in table 1 are satisfactory for the purposes of approximate data.

The surface area of each skin region was estimated by applying adhesive tape to the smaller areas and coordinate paper to the larger areas and then counting squares. These estimates of area were sufficiently accurate for our purposes as indicated by a satisfactory agreement with DuBois standards on comparable subjects (2).

The subject of the experiment arrived in the laboratory at 7:00 a.m. without breakfast, undressed and lay quietly on a cot. Sampling of skin pulses, skin and rectal temperatures, and of oxygen consumption, began about 90 minutes later. Room temperatures were about 25° to 27°C., relative humidity about 40, air movement not noticeable. The subjects remained comfortable throughout the observations; however, *W. R.* felt cool and was not far removed from shivering; *V. D. G.* felt comfortably warm. Differences in the average cutaneous blood flow in the two subjects agree with these subjective differences. The subjects were lean, active young men.

The values for the mean cutaneous blood flows as estimated photoelectrically in the two subjects of table 1 were, respectively, 0.016 and 0.028

cc/cm<sup>2</sup>/min. These values are, respectively, three and five times higher than the average values reported with the thermal method but are not greatly out of line with flows in the upper range of values (2).

There are several possible explanations of the differences between the photoelectric and the thermal measurements of total cutaneous blood flow.

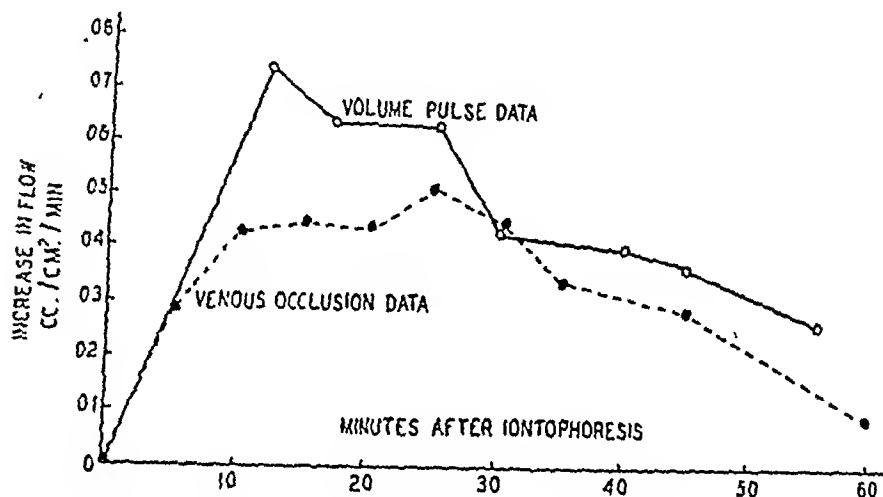


Fig. 1. INCREASE IN FOREARM skin flow after mecholyl iontophoresis.

First, errors may occur due to a possibly nonrepresentative sampling of skin blood flows by the photoelectric recordings of the skin pulses. We doubt that this is a major source of error since we consistently obtained in all subjects higher total flows than would be indicated from the thermal data.

Second, in the expression ( $F = \frac{HI}{MR - M_s} - k$ ), for calculating the skin blood flow from the thermal data (2),  $k$  is the numerical value for the thermal conductivity of the superficial tissues when the thermal gradient extends linearly over a distance of 20 mm. from the interior to the surface of the skin. An increase in the superficial blood flow will affect the linearity of this gradient as well as the depth of tissue over which it extends and thus decrease the numerical value of  $k$ . Assuming a constant value for  $k$  at this time will lead to lower values for the skin blood flow than what may actually be the case and also will indicate incorrectly the first increase in skin blood flow on warming the subject. Further, the assumed A-V difference in temperature may not hold, particularly in the extremities (6).

Third, the flow equivalent of the skin pulse either may be a function of the rate of blood flow, decreasing as the vessels constrict, or it may vary in different skin regions. Preliminary data on chilled subjects in which extremely low finger flows (about 0.005 cc/cm<sup>2</sup>/min.) were elicited suggest

that the approximately linear relation between flow and skin pulse, which seems to hold in the flow ranges usually encountered in the finger pad, is not applicable at these very low flows and that in fact the flow equivalent of the skin pulse does decrease at extremely low flows. We have no direct information on the applicability of this observation to vascular areas other than the finger, as no other method of fractionating the total cutaneous blood flow is available. If, however, the flow equivalent of skin pulses on the trunk were found to be significantly lower, the photoelectric measurement of the total cutaneous flow would be brought into better correspondence with the thermal and helium uptake data.

Inspection of table 1 reveals that the mean basal cutaneous blood flow as estimated photoelectrically may be approximated from recordings of the skin pulses on only the forearm. This is indeed convenient as a systematic sampling of the skin pulses over the entire body is not only very laborious but also impracticable when moderately rapid changes in the skin circulation occur as in the development of hyperthermia. Preliminary observations indicate that the increases in forearm flow in hyperthermia mirror quite well the increases in total cutaneous blood flow; this statement does not apply, however, to the hands and feet, in which the dilatation occurs earlier and more abruptly and reaches its maximum earlier than in other areas.

One may also note from table 1 that the major regional differences and also the total cutaneous blood flow may be approximated from recordings of the skin pulses in only four areas which happen to be conveniently accessible; the skin flow in the trunk, leg and arm from recordings of the skin pulses in the leg; foot flow from the toe pad pulses divided by 2.5; hand flow from the finger pad pulses divided by 2.5; and face flow from the cheek pulses. The values so obtained are not as accurate as those secured by a systematic topographical exploration of the skin surface, but they do have significance and are useful in observing regional differences in the behavior of the skin circulation.

#### *Regional Differences in the Basal Cutaneous Blood Flow*

Topographical differences in the rates of cutaneous blood flows are exhibited in table 1. The differences are considerable; thus, in *subject V. D. G.*, the range in blood flow was from 0.27 to 0.015 cc/cm<sup>2</sup>/min. in the finger pad and thigh, respectively. Inspection of table 1 reveals that the various skin areas may be grouped into two divisions: one exhibiting a relatively high rate of blood flow and including the skin of the head and the palmar and plantar surfaces; the other showing a relatively low rate of blood flow and including the skin of the forearm, trunk, leg and thigh. It will also be noted that the rate of blood flow in the low rate areas is approximately the

TABLE 1. FRACTIONATION AND ESTIMATION OF THE TOTAL CUTANEOUS BLOOD FLOW UNDER BASAL CONDITIONS<sup>1</sup>

SKIN SURFACE	AREA		RATE OF BLOOD FLOW		BLOOD FLOW		% OF TOTAL CUTANEOUS BLOOD FLOW	
	W. R.	V. D. G.	W. R.	V. D. G.	W. R.	V. D. G.	W. R.	V. D. G.
	cm <sup>2</sup>	cm <sup>2</sup>	cc/cm <sup>2</sup> /min.		cc/min.	cc/min.		
Hand.....	372	439	.036	.094	13.25	41.58	9.5	15.6
Finger pad.....	40	40	.072	.27	2.88	10.80		
Palm.....	142	158	.037	.14	5.25	22.10		
Dorsum.....	190	241	.027	.036	5.12	8.68		
Forearm.....	775	703	.012	.034	9.30	23.39	6.65	8.74
Arm.....	555	782	.0032	.022	1.78	17.20	1.27	6.43
Foot.....	687	666	.0246	.0336	16.84	22.37	12.05	8.37
Dorsum.....	463	418	.018	.018	8.34	7.52		
Plantar.....	194	218	.036	.055	7.00	12.00		
Toe pads.....	30	30	.050	.095	1.50	2.85		
Leg.....	1361	1487	.013	.022	17.70	32.70	12.65	12.25
Thigh.....	1486	1551	.0103	.015	15.30	23.20	10.95	8.67
Trunk.....	3291	3683	.0122	.0224	40.33	82.60	28.9	29.80
Shoulder.....	751	796	.0160	.022	12.00	17.65		
Back, breast, abdomen.....	1657	2092	.0118	.020	19.50	41.90		
Buttocks.....	883	795	.010	.029	8.83	23.05		
Head.....	240	252	.105	.098	25.34	24.65	18.15	9.23
Forehead.....	61.5	81.0	.072	.11	4.42	8.90		
Cheek.....	101	126	.111		11.20	11.35		
Nose.....	15.5		.20	.09	3.10			
Chin.....	15.0		.148		2.22			
Ear.....	47.0		.094	.098	4.40	4.40		
Totals and Means.....	8,767	9,563	.016	.028	139.84	267.69		

<sup>1</sup> Body surface areas: W. R.—1.82 sq. m.; V. D. G.—2.05 sq. m.

same, suggesting that the vascular anatomy of most of the body's skin is uniform with respect to the number and size of the vessels. This point is developed further in the following section. Deviations from this statement are exhibited in the skin of the feet, hands and face. These surfaces comprise only 7.3 per cent of the total skin area; yet, 27 per cent of the total basal cutaneous blood flow occurs in these areas. The exceptionally high basal rates of flow in these latter areas suggest that vascular observations conducted on the feet and hands often may not be applicable to other cutaneous areas.

*Regional Differences in Maximal Cutaneous Blood Flows*

The regional differences in the rates of skin blood flow obtaining under basal conditions are exhibited also in instances of maximal dilatation in the skin, which may be elicited by the local iontophoresis of a powerful dilator drug such as histamine or mecholyl into a small skin area. The resulting increases in blood flows in various skin areas (with the exception of the palmar and plantar surfaces of the hands and feet) are not exceeded by increases which have been elicited by other means, such as heat. The results of such experiments are summarized in table 2, which includes the effects of generalized heating. One will note that the various skin regions may be divided again into two groups: regions of high maximal flows (fingers, toes, face and skin) and of low maximal flows (trunk, arms and legs), and further, that in the latter group the maximal flows are approximately the same in the various regions. We interpret these data as measuring the maximal vascular bed available through the relaxation of vascular tone. The absolute magnitude of the vascular bed is therefore quantitatively uniform in the skin of the trunk, legs and arm. The considerably higher maximal flows in face skin, finger and toe pads imply a correspondingly larger vascular bed in these skin regions.

The validity of these measurements may be examined by comparison of our data with calculations which may be made from measurements of forearm flow by the venous occlusion method after iontophoresis of mecholyl and of histamine (7). The blood flow increased in these latter experiments from a control level of 1.2 cc/100 cc forearm/min. to 4 cc/100 cc/min. It is probable that all of this increase occurred in the skin, although direct evidence for this statement is not available. It is also probable that the dilatation is maximal, since that produced by histamine is quantitatively similar to that induced by the choline derivative. It would be remarkable indeed if the dilatation induced by these two drugs were both submaximal and equal.

A recalculation of the increase in forearm flow in terms of the surface area of the forearm yields a value of 0.054 cc/cm<sup>2</sup>/min. This value is about half of the average increases which have been observed with the photoelectric plethysmograph. This difference may be due in part to a comparison of the average increase in our series of 9 subjects with the results of a single experiment in the venous occlusion series, since in three of our subjects the increase in flow was very nearly the same as that calculated from the venous occlusion data.

The comparison of the photoelectric estimations of increases of flow in forearm skin with those calculated from venous occlusion data gains insignificance if the increases in skin flows are charted against time as is done in

figure 1. The course of the two experiments is comparable. Similar correlations appear in comparing the increases in skin flow which result from histamine iontophoresis.

### DISCUSSION

It is convenient to summarize here the evidence which supports the argument that our photoelectric procedure for the estimation of skin blood flows yields data of the correct order of magnitude and sufficiently close to

TABLE 2. TOPOGRAPHICAL DIFFERENCES IN THE MAXIMAL SKIN BLOOD FLOWS ELICITED BY HEAT OR BY IONTOPHORESIS OF HISTAMINE OR OF MECHOLYL

Skin region	Average maximal blood flow cc/cm <sup>2</sup> /min.	Skin region	Average maximal blood flow cc/cm <sup>2</sup> /min.
Finger pad	0.60	Forearm	0.15
Toe pad	0.46	Arm	0.15
Forehead	0.41	Shoulder	0.19
Cheek	0.44	Leg	0.15

the actual values to make this method practical for the study of various physiological mechanisms operating on the skin circulation.

a) The correlation between the amplitude of the photoelectrically recorded cutaneous volume pulse and the cutaneous blood flow has been shown to hold in the finger under normal circumstances (5) and in the presence of vascular pathology (8), providing blood flow rates are above 0.2 cc/cm<sup>2</sup>/min.

b) The data in this paper show that this correlation may be employed to estimate the rates of blood flow in skin regions other than the finger. These data also provide a basis for calculating the total cutaneous blood flow. The estimate of the latter yields reasonable values. Their absolute accuracy can not be appraised until an error-free method of measuring skin blood flows in man has been developed.

c) The estimation of skin blood flows during maximal dilatation from the amplitude of the photoelectrically recorded cutaneous volume pulse also results in data which appear to be reasonable.

The refutation of this argument involves the following quantities, the absolute magnitudes of which are open to question: a) the average value of the rate of cutaneous blood flow as based on thermal data; b) the volume equivalent of the photoelectrically recorded skin pulse; c) the flow equivalent of the cutaneous volume pulse.

Reasons have been offered in an earlier paper (5) to show why the volume equivalent of the photoelectrically recorded skin pulse may be transferred to other skin areas; however, direct estimates of the validity of this procedure are not available; the degree to which this is possible bears on an attempt to correlate the volume pulses and blood flows. The linearity of this relation may not hold at low flows due to unequal constrictor effects on

pulsating arteries and the arterioles, where classical opinion locates the chief resistance to flow. The histological observations of Richins (9, unpublished) on the vasomotor picture in rapidly frozen tissue preparations suggest such unequal constrictor effects. If this is true, blood flow may decrease relatively more than the skin pulse at very low flows.

#### SUMMARY

The basal blood flows in the various skin regions of the body were estimated from the consecutive recordings by the photoelectric plethysmograph of the cutaneous volume pulses in these skin regions. Rates of blood flow were calculated by applying to these records the flow equivalent of the skin pulse as estimated previously on the finger. The total cutaneous blood flow was obtained from the sum of the flows in the various skin regions. The values thus estimated were somewhat higher than those which have been calculated from thermal data but were still of the same order of magnitude (160–250 cc/M<sup>2</sup>/min.). Reasons for the differences between the values for skin blood flows as derived from thermal and skin pulse data are discussed.

Regional differences in the basal rates of cutaneous blood flow are exhibited in the data. Flows are approximately uniform and equal in the skin of the trunk, arm and leg but considerably higher in the palmar and plantar surfaces and in the skin of the face and head.

Regional differences in the maximal rates of cutaneous blood flow (maximal dilatation as elicited by heat or by the iontophoresis of histamine or of mecholyl) follow the same general regional pattern as shown in the basal rates of flow and appear to be set by the vascular morphology (size and number of vessels).

An argument is briefly summarized to show that the estimation of the rates of cutaneous blood flows from the photoelectric recordings of the skin volume pulses is sufficiently correct to have value in the study of vascular reactions in the skin.

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# *Influence of Hemorrhage, Albumin Infusion, Bed Rest, and Exposure to Cold on Performance in the Heat<sup>1</sup>*

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IT HAS BEEN SUGGESTED that the improvement in physical performance manifested during acclimatization to heat (1-3) may be due to increased cardiovascular efficiency (2, 4, 5). One might hypothesize further that enlargement of blood volume which normally occurs during acclimatization (5-9) is an important factor allowing for the higher efficiency of the cardiovascular system. Others have speculated previously on this possibility but have not tested the hypothesis by direct experiment (4, 5). In the present study, we recorded the ability of several young men to carry out various physical activities in the heat during the course of experiments in which blood volume was altered artificially to an extent that occurs normally during acclimatization. Published studies (10, 11) of performance following alteration in blood volume (by venesection) were not designed to furnish information with regard to acclimatization, and, in most of these investigations, ambient temperature was not controlled.

## OUTLINE OF EXPERIMENTS

In the first group of experiments, 4 young men<sup>2</sup> were scored on ability to perform simple tasks under standard warm conditions (33°C., D.B., 28-29°C., W.B., wind velocity 50 cm/sec.) after having spent 24 to 28 hours in the hot room. The subjects reported at 8 a.m., dressed themselves in shorts, undershirts and sandals, and remained in the room until the following morning. An adequate diet was provided. Testing began at 8 a.m. on the second morning (under basal conditions) and was usually completed before 11 a.m. The tasks, consisting of active standing (Crampton Test), passive standing on a tilt table and pedalling a bicycle ergometer for 20 minutes, were performed under basal conditions and always in the same order. (Several tests were employed in order to obtain more reliable estimates of the effects of our experimental procedures.) Two or three experiments were scheduled each week during the Summer of 1947. This schedule presumably induced a partial but incomplete degree of acclimatization to the temperature employed for testing.

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<sup>2</sup> These men were junior and senior medical students. All were in their early or middle twenties. Heights and weights were as follows: A, 165 cm., 57 kg.; B, 180 cm., 69 kg.; D, 173 cm., 66 kg.; K, 175 cm., 78 kg. Subject A is a Jamaican; the others, predominantly Anglo-Saxon.

Control studies alternated with experiments designed to determine the influence of exposure to cold, bed rest and hemorrhage on ability to perform. The effects of cold and bed rest were studied, since these have been reported to decrease blood volume (9). In the experiments on exposure to cold, the temperature of the room was maintained at 20°C., D.B., 18°C., W.B., from the beginning of the period (8 a.m.) to 5 a.m. the following morning, at which time the room was warmed to the standard testing temperature. In the experiments on bed rest, subjects remained in bed for the 24 hours previous to testing. Venesection (500 cc.) in the hemorrhage experiments was performed 10 to 12 hours (9 p.m.) before the routine morning tests. Additional tests (on tilt table and bicycle ergometer) were made 30 minutes to two hours following venesection, and similar tests for comparative purposes were made at the same time of the day during the previous control experiment. Observations were continued for a week or more following hemorrhage.

Serum protein concentrations (by specific gravity), hemoglobin concentrations and hematocrit values were determined on samples of blood obtained from the subjects before they arose each morning. Total hemoglobin (using carbon monoxide) of each subject was determined periodically. A detailed account of the methods used has been published recently (9).

Additional observations were made subsequently (Fall of 1947) with a group of somewhat older subjects (the authors of this paper)<sup>3</sup>. These men were unable, because of other duties, to remain for an entire day in the controlled temperature room and so were tested an hour or so after entering the hot room. All tests were performed in the morning under basal conditions. A period of training in the tests to be employed was carried out for several weeks before the experiments were begun. This precaution was also taken in the first group of experiments. Unfortunately, shortly after the first group of experiments was begun, two of the trained subjects felt that the experiments were too severe and they were replaced by relatively untrained men.

Only the tilt table and Crampton tests were employed in the second group of experiments. Each subject performed the two tests in succession and then performed them again after lying down for an hour. The rest period was employed for the purpose of reproducing as nearly as possible the condition of the first test. In the first two experiments, both sets of tests were done under control conditions. In the third experiment, serum albumin (100 cc. of a 25 per cent solution<sup>4</sup>) was infused in the interval between the two sets of tests. In a similar fashion, venesection (200 cc.) was performed during the fourth experiment. The fifth experiment, carried out two to four days following venesection, was made to determine whether subjects had recovered from hemorrhage. The final experiment was performed at a comfortable temperature (24°C., D.B., 21°C., W.B.) for the purpose of determining the magnitude of the effect of environmental temperature. Tests were not performed in duplicate in the final two experiments.

#### TESTING PROCEDURES

*Crampton Test.* This test was performed in the manner originally described by Crampton (12) with the exception that recumbent pulse rates and blood pressures were obtained before subjects arose to start the

<sup>3</sup> These were staff members. Ages, heights, and weights were as follows: B, 30 yrs., 180 cm., 68 kg.; W, 30 yrs., 171 cm., 66 kg.; N, 27 yrs., 182 cm., 82 kg.; S, 38 yrs., 172 cm., 62 kg. All are predominantly Anglo-Saxon.

<sup>4</sup> Supplied by the American Red Cross.

TABLE 1. PERFORMANCE DATA OBTAINED IN THE MORNING UNDER RESTING-FASTING CONDITIONS IN THE FIRST GROUP OF EXPERIMENTS<sup>1</sup>

SUBJ.	DATE												MEAN CON.	
	7-22	7-24	7-26	7-29	7-31	8-2	8-5	8-8	8-12	8-15	8-19	8-22		
	Conditions									Recovery from hemorrhage				
	con.	cold	con.	rest	con.	cold	con.	cold and rest	con.					

*a. Crampton Scores*

A.....	+50	+15	+90	+35	+45	+90	+45	+30	+55	+25	+30	+50	+57
B.....	+30	+65	+95	+70	+80	+60	+65	+40	+80	+50	+75	+65	+70
D.....	—	—	+45	+75	+80	+35	+25	+10	+75	+10	+50	+20	+56
K.....	—	—	—	—	+30	+20	+40	-40	+15	-30	+30	-5	+28
			+93		+68								
Mean.....	+40	+40	+77	+60	+59	+51	+44	+10	+56	+14	+46	+33	(+53)

*b. Bicycle Ergometer, 15-20 Minute Pulse Rates*

A.....	168	162	153	134	133	146	162	175	182	192	147	149	156
B.....	127	118	122	136	133	123	126	135	132	137	138	129	128
D.....	—	—	150	142	134	134	133	145	143	141	145	133	140
K.....	—	—	—	—	135	129	136	147	126	132	130	124	132
			128		133								
Mean.....	148	140	135	137	134	133	139	151	146	151	140	134	(140)

*c. Tilt Table, 15-20 Minute Pulse Rates*

A.....	108F	124F	91	98	97	115	104	122	115	132F	115	106	103
B.....	113	116F	105	121	109	115	113	123	113	122	116	110	111
D.....	—	—	103	97	91	107	95	111	103	119	116	116	98
K.....	—	—	—	—	128	126	136F	145	129	131	132	119	131
			98		99								
Mean.....	111	120	100	105	107	116	112	125	115	126	120	113	(111)

*d. Resting Pulse Rates Before Tilling*

A.....	85	94	75	72	72	68	73	86	81	80	70	70	77
B.....	81	84	73	80	77	89	79	83	73	81	86	82	76
D.....	—	—	65	55	62	62	58	67	64	71	66	73	62
K.....	—	—	—	—	91	101	70	105	95	99	75	81	85
			74		70								
Mean.....	83	89	71	69	76	80	70	85	78	83	74	77	(75)

<sup>1</sup> Crampton scores were obtained on first arising in the morning; otherwise the procedure corresponded with the original description of the method (12). Pulse rates on the bicycle ergometer and tilt table are means of values obtained at 15 and 20 minutes and at 15, 17 and 19

day's activities. The test is scored rather arbitrarily from changes in pulse rate and systolic pressure. The score increases with improving performance.

*Tilt Table.* Following the Crampton test, the subjects, while still in the basal state, mounted the table and lay down supine. A board was adjusted to give firm support to the feet; a cotton tie was secured around the chest and electrodes for recording electrocardiograms were attached. The subjects remained horizontal until blood pressure readings and pulse rates were stable on two successive odd minutes. This usually required about five minutes. On command, the table (with subject) was tilted to an angle of  $70^{\circ}$  from the horizontal. Pulse, blood pressure and respiration were taken every other minute for 19 minutes. At the 20th minute, subjects were tilted back to the horizontal position and recordings were continued for five minutes. While the subjects were on the table, they were instructed to remain motionless and to breathe normally. When upright the subjects were questioned from time to time regarding their condition. If fainting appeared imminent at any time, subjects were returned to the horizontal position.

*Bicycle Ergometer.* Following the tilt table, the subjects had rectal temperatures taken and were weighed (nude). They then pedalled a bicycle ergometer for 20 minutes (in time with the metronome). At five-minute intervals, pulse and respiration rates were recorded. Promptly after the 20th minute, rectal temperatures were again taken. During this time the subjects dried themselves and were then reweighed. The rate of pedalling and resistance of the brake were such that the least fit subject had difficulty completing the period.

In summarizing our data, we have presented the Crampton scores and the final pulse rates (average rates between 15 and 20 minutes) obtained in tests on the tilt table and bicycle ergometer. In cases of fainting on the tilt table, the highest pulse rate attained in the vertical position is used, since fainting is often accompanied by a slowing of the heart. Resting pulse rates before tilting are recorded for reference. Accurate measurements of blood pressure were not obtainable on subjects in the tilted position because

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minutes, respectively. In cases of fainting on the tilt table (F), the highest pulse rate attained is given. Resting pulse rates are those obtained on the tilt table prior to tilting. All values are in chronological sequence. The final column shows the mean control (con.) values for each subject. Two sets of mean values are given in the columns for 7-26 and 7-31. This is necessary for comparative purposes, because of variability in the number of subjects participating in experiments at these times. The means for control mean values are parenthesized, for they are based upon only the experiments in which all subjects participated (last 3 control experiments). Experimental conditions prior to testing are indicated at the top of each column (see text for further details). Venesection (hemorrhage) was performed on the evening of 8/14. The standard testing temperature was  $33^{\circ}\text{C.}$ , D.B.,  $28-29^{\circ}\text{C.}$ , W.B.

of *a*) the marked variation of blood pressure with respiration and *b*) the faintness of the sounds. Respiration rates on the tilt table were generally quite variable and consequently are not a suitable index for our purpose. Rectal temperatures and sweating rates obtained in tests on the bicycle ergometer were in most instances not influenced greatly by our experimental procedures and are, therefore, not presented.

Performance in control periods immediately preceding and succeeding an experimental period is presumably the most reliable control for each experiment of the first group of experiments. In the second group of ex-

TABLE 2. PERFORMANCE DATA OBTAINED IN THE EVENING UNDER NONBASAL CONDITIONS (FIRST GROUP OF EXPERIMENTS)<sup>1</sup>

SUBJ.	BICYCLE ERGOMETER		TILT TABLE		RESTING PULSE		RESTING BLOOD PRESSURE	
	Conditions							
	con.	hem.	con.	hem.	con.	hem.	con.	hem.
A.....	153	184	101	137	72	86	108/68	98/58
B.....	128	143	115	132F	91	99	112/76	124/84
D.....	128	162	94	132F	77	72	98/80	116/76
K.....	117	168	125	164F	78	108	120/68	106/68
Mean.....	132	164	109	141	80	91	110/73	111/72

<sup>1</sup> Control values (con.) were obtained on the evening of 8/11. The other values were obtained 0.5 to 2 hours following hemorrhage on 8/14.

periments, control tests made an hour before the experimental tests serve as controls. In this case our data indicate that a small correction should be made, for, when a control test was scheduled in place of an experimental test, superior performance was almost uniformly observed in the second control test (see first two experiments of table 3).

## RESULTS

Following bed rest, subjects of the first group of experiments performed more poorly on the average in all three tests than they did in the immediately previous and subsequent control experiments, and the two more thoroughly trained subjects (*A* and *B*) were perfectly consistent in doing so, though, in some instances, the differences were slight (table 1). In both experiments on exposure to cold, average performance on the tilt table was poorer than in the corresponding control experiments; however, performance in the other two tests was not altered consistently in any direction. In the experiment in which exposure to cold and confinement to bed were combined, all subjects performed more poorly than they did in either control experiment, with one exception (subject *A*, bicycle ergometer). Approximately the same marked degree of deterioration in ability was

observed 12 hours after removal (by venesection) of 500 cc. of blood, with a return toward normal levels a few days later. The immediate effects of hemorrhage (30 minutes to two hours following venesection) were even greater. Average pulse rates on the tilt table and bicycle ergometer exceeded values in control tests by 31 and 32 beats per minute, respectively;

TABLE 3. PERFORMANCE DATA OBTAINED IN THE MORNING UNDER RESTING, FASTING CONDITIONS IN THE SECOND GROUP OF EXPERIMENTS<sup>1</sup>

SUBJECT	DATE										MEAN	
	11/5-6		11/13-14		11/17-18		11/20-21		11/24	11/25		
	Condition										con <sub>1</sub>	con <sub>2</sub>
	con.	con.	con	con.	con.	inf.	con.	hem.	post hem.	cool		

*a. Crampton Scores*

<i>Bi</i>	+10	+0	—	-20	-55	-13	-18	-68	-13	+35	-21	-10
<i>W</i>	+43	+60	+8	+43	+64	+63	+95	+40	+33	+45	+53	+52
<i>N..</i>	+45	+73	+25	+60	+58	+83	+63	+40	+33	+93	+48	+67
<i>S...</i>	+35	+43	-10	+15	+35	+38	-5	+18	+15	+48	+14	+29
Mean .	+33	+44	—	+25	+26	+43	+34	+8	+17	+55	+24	+35

*b. Tilt Table, 15-20 Minute Pulse Rates*

<i>Bi</i> . . . .	98F	95	108F	103	110F	92	103	105	105	71	105	99
<i>W</i> . . . .	94	93	89	89	97	85	89	83	99	75	92	91
<i>N.....</i>	90	83	86	82	86	81	93	94	103	69	89	83
<i>S . . . .</i>	140F	132F	123F	139F	125	118	123F	126F	126F	99	128	136
Mean	106	101	102	103	105	94	102	102	108	79	104	102

*c. Resting Pulse Rate Before Tiltting*

<i>Bi</i>	48	46	50	52	56	52	50	54	52	44	51	49
<i>W</i>	64	58	64	66	62	58	58	56	63	63	62	62
<i>N</i>	66	70	60	60	64	64	63	60	69	51	63	65
<i>S .</i>	78	76	80	78	78	85	72	78	76	62	77	77
Mean	64	63	64	64	65	65	61	62	65	55	63	63

<sup>1</sup> In the first four sets of experiments, duplicate determinations were made on two subjects on each of two successive mornings. For example, *Bi* and *W* were tested on 11/5 and *M* and *S* were tested on 11/6. On 11/24 and 11/25, single determinations were made on all 4 subjects. The first two sets of experiments were control experiments. In the third experiment (11/17-18) serum albumin (100 cc. of a 25 per cent solution) was infused (inf.) during the rest period between duplicate determinations. In the fourth experiment venesection (200 cc.) was performed between determinations (hem.). The experiment on 11/24 was made under standard testing conditions to determine the degree of recovery from hemorrhage. The experiment on 11/25 was made in a cool room (24°C., D.B., 21°C., W.B.) to determine the influence of environmental temperature on performance. Means of the first (con<sub>1</sub>) and second (con<sub>2</sub>) control values obtained on a single day are shown in the final two columns.

moreover, 3 of the 4 subjects fainted on the tilt table while none of the subjects fainted in the control test (table 2). Mean resting pulse rate prior to tilting was also considerably above the control value, but resting blood pressure remained unchanged.

In the second group of experiments, performance on the tilt table, as judged by pulse rates, improved greatly following infusion of serum albumin in an amount equivalent to 500 cc. of plasma (table 3). However, a beneficial effect of infusion was not demonstrated in the case of the Crampton test. Though average Crampton score was better than in the control tests of that day, the improvement was not much greater than

TABLE 4. HEMOGLOBIN AND SERUM PROTEIN CONCENTRATIONS (FIRST GROUP OF EXPERIMENTS)<sup>1</sup>

SUBJECT	DATE												MEAN CON.
	7-22	7-24	7-26	7-29	7-31	8-2	8-4	8-8	8-12	8-15	8-19	8-22	
	Condition									Recovery from hemorrhage			
	con.	cold	con.	rest	con.	cold	con.	cold and rest	con.				
<i>a. Hemoglobin Concentration</i>													
A.....	14.0	15.4	14.2	14.9	14.5	15.5	15.1	16.1	14.8	13.3	13.5	13.8	14.7
B.....	15.2	15.0	14.5	15.4	14.6	14.9	15.1	15.8	14.7	13.4	12.8	13.6	14.8
D.....	—	—	14.9	15.7	14.6	15.4	15.4	16.1	15.2	13.8	13.4	13.4	15.3
K.....	—	—	—	—	16.5	16.3	16.4	17.3	15.9	14.5	14.5	14.6	16.3
Mean.....	15.1	15.2	14.4	15.3	14.6	15.1	15.5	15.5	16.3	15.2	13.8	13.6	13.9 (15.2)
<i>b. Total Circulating Hemoglobin</i>													
Mean.....	106	94	98	94	106	102	101	99	101	91	91	95	102
<i>c. Serum Protein Concentration</i>													
A.....	6.1	6.3	—	6.1	6.0	6.2	6.1	6.6	6.1	5.7	5.8	6.0	6.1
B.....	6.4	6.3	5.9	6.2	6.0	5.9	6.1	6.5	6.0	5.8	5.8	6.0	6.1
D.....	—	—	5.8	6.0	5.8	5.8	6.0	6.2	—	5.6	5.6	5.6	5.9
K.....	—	—	—	—	6.6	6.4	7.0	6.9	6.5	6.2	6.4	6.4	6.7
Mean.....	6.3	6.3	—	6.1	5.9	6.1	6.3	6.6	—	5.8	5.9	6.0	(6.2)

<sup>1</sup> Values are from samples of blood obtained before subjects arose in the morning. Total circulating hemoglobin was determined (by carbon monoxide) on one subject each day that the experiments were performed, employing all 4 subjects in rotation; the values are expressed as percentage of the total circulating hemoglobin of each individual, as determined from several values obtained prior to the start of these experiments. Means of values obtained in control experiments on each subject are shown in the last column. The parenthesized values are based upon only the control experiments (last three) in which all subjects participated.

might have been expected in a second control test (see TESTING PROCEDURES). The effect of infusion on tilt table performance was transient, however, for performance was again near control levels a few days later. Pulse rates on the tilt table one-half hour or so following hemorrhage were nearly identical with those obtained in the control test. On the other hand, average Crampton score was one of the lowest values obtained for these subjects and was well below the value obtained in the control experiment of that day. Moreover, a few days later pulse rates on the tilt table were moderately elevated and Crampton scores were still low. The data suggest that performance was adversely affected to a moderate degree by the venesection but are discrepant in that pulse rates on the tilt table were not elevated in tests performed immediately after hemorrhage.

#### DISCUSSION

*Lack of Correlation of Performance with Hemoglobin Concentration.* Because of the rôle of hemoglobin as an oxygen carrier one might suppose that performance would vary directly with the level of hemoglobin concentration, but this was not the case in our study. In many instances, e.g., following bed rest or exposure to cold, performance tended to be poor while hemoglobin concentration was above control values (table 4). On the other hand, performance was also poor for some time following hemorrhage when hemoglobin concentration was below control levels. Comparison of data obtained 12 hours after venesection of 500 cc. with those obtained following bed rest and exposure to cold affords a striking example of the lack of correlation between performance and hemoglobin concentration. Performance was approximately the same in both cases, but hemoglobin concentration following bed rest and exposure to cold was 18 per cent greater than hemoglobin concentration 12 hours after venesection (table 4). It seems likely that a correlation may exist in cases of other types of performance and may be more evident at comfortable environmental temperatures. For example, Karpovitch and Millman (10) found performance in endurance exercise to be reduced for 10 to 20 days following blood donation. In this case, performance recovered in a period of time corresponding with that required for replacing much of the donated hemoglobin. In our study, the body was taxed to maintain adequate circulating blood volume both because of the marked peripheral vasodilation present in the heat and by the nature of some of the tests of performance, e.g., passive standing. Consequently it might be expected that performance in our experiments may have been determined to some extent by the level of blood volume.

*Correlation of Performance with Blood Volume.* Unfortunately, our method for determining blood volume by carbon monoxide is not sufficiently



accurate to determine easily, i.e., by comparison of two single determinations, blood volume changes of less than about 5 to 10 per cent. It was only possible to determine the blood volume of a single subject on any one day in the first group of experiments. While these few values are useful in showing the absence of any trend in level of total hemoglobin up to the time of venesection, they are not sufficiently reliable to predict small changes in blood volume. Consequently, in these experiments it is only possible to infer the magnitude of change from values for hemoglobin concentration by

TABLE 5. HEMOGLOBIN CONCENTRATION AND PERFORMANCE ABILITY IN CONTROL EXPERIMENTS<sup>1</sup>

	+	-	TOTALS
Performance			
+	(12.7) 8	(11.3) 16	24
-	(14.3) 19	(12.7) 8	27
Totals.....	27	24	51

<sup>1</sup> A four-fold table from data obtained in controls of the first group of experiments showing the association of concentrations of hemoglobin above mean value with performance ability. In preparing the table, each individual was considered separately with reference to Crampton score, pulse rate on ergometer and pulse rate on tilt table and the results were summated. Observed frequencies are given below theoretical frequencies (in parentheses). Chi square equals 6.98 ( $p = 0.008$ ) for this distribution.

assuming total circulating hemoglobin remained constant in quantity. Evidence is accumulating that this commonly made assumption is generally consistent with data obtained over short periods of time in blood volume studies on healthy young men (8, 9).

Estimates of changes in blood volume made in this way indicate a decrease of 1 to 3 per cent following exposure to cold, 5 per cent following bed rest and 6 per cent following bed rest together with exposure to cold. In a general way, these estimates of magnitude of decrease in blood volume parallel the degree of deterioration in performance (see RESULTS). Blood samples were not taken at the time of tests made an hour or so following hemorrhage in the first group of experiments. However, it may be assumed that blood volume was lowered by somewhat less than 10 per cent (the extent of the venesection). For, although an insignificant regeneration of plasma protein or erythrocytes would have occurred in this short time and large stores or reservoirs of red cells are not believed to exist in normal men (13), entrance of protein-free fluid would effect a partial restoration of blood volume (14, 15). In agreement with this probably large blood-volume

deficit is the marked deterioration in performance observed. Twelve hours later, blood volume was again close to control levels as indicated by the fact that hemoglobin concentration had declined approximately 10 per cent. However, at this time protein concentration was 7 per cent below control levels. Now it is unlikely that the extra fluid responsible for dilution of the plasma protein is of comparable value to a similar volume of fluid containing a normal concentration of protein. If comparison is made upon the basis of equal concentrations of plasma protein, blood volume may be considered to have been below control levels. And, as has already been noted, performance was poor at this time. (One other case in which there was appreciable change in concentration of plasma protein requires discussion. Following bed rest and exposure to cold, an increase in protein concentration of 6 per cent occurred while hemoglobin concentration also increased 6 per cent. Had the increase in hemoglobin concentration been due solely to removal of protein-free fluid, protein concentration would have increased approximately 11 per cent. Consequently, the conclusion that blood volume was decreased in this case is reached whether comparison is made on the basis of actual change in hemoglobin concentration or on the basis of the change in hemoglobin concentration that would have occurred had protein concentration remained constant.) During subsequent tests (four to eight days following venesection) in which performance was near control levels, blood volume was presumably above normal values. For appreciable regeneration of hemoglobin would have occurred during these few days, but there was not any increase in hemoglobin concentration. Protein concentration approached normal during this time.

In the second group of experiments, blood volume changes were induced only by venesection and infusion, and testing was performed immediately afterwards. The blood volume deficit following venesection was presumably somewhat less than the amount of blood removed (5 per cent) because of entrance of protein-free fluid (see above). And in agreement with the results of the first group of experiments there was evidence that performance was affected adversely. In the infusion experiment, only 100 cc. of albumin solution was administered; however, the solution was five times the normal concentration. Consequently blood volume was increased by more than 2 per cent but probably less than 10 per cent. In this case we obtained definite evidence for improvement in performance. A final sample illustrating the dependency of performance on blood volume is found in the control data of the first group of experiments in which there exists a significant inverse correlation ( $p = 0.008$ ) between goodness of performance and hemoglobin concentration (table 5). Presumably, variation in blood volume was responsible in part for variation in level of performance in control experiments.

If our results are interpreted correctly, it may be stated that small changes in blood volume (less than 5 per cent in some instances) affect rather greatly the ability of partially acclimatized individuals to perform physical tasks under warm conditions. Blood volume is reported to increase to a similar or greater extent during acclimatization or adaptation to warm environments. For example, we found an increase of approximately 5 per cent to occur between the first and sixth day of residence in the heat (9). In another recent study (8), blood volume was estimated to increase by 10 per cent or more between the first and third days of exposure. Earlier studies, for the most part, have also indicated appreciable increases in blood volume under similar circumstances (5-7). It may be noted further that the time course of increase in blood volume (9) resembles very closely the time course of acclimatization to heat (1, 2). Both events proceed rapidly during the first few days and are nearly complete by the end of a week. These considerations favor the view that an increase in blood volume may be one of the important adjustments in acclimatization to heat.

#### SUMMARY

1. The ability of 4 young men to perform in the heat ( $33^{\circ}\text{C}$ ., D.B.,  $28-29^{\circ}\text{C}$ ., W.B.) certain simple physical tasks (active and passive standing, pedalling a bicycle ergometer) was tested following short (24 hours) periods of bed rest, venesection of 500 cc., exposure to cold ( $20^{\circ}\text{C}$ ., D.B.,  $18^{\circ}\text{C}$ ., W.B.) and in control experiments. In all cases, subjects remained in the controlled temperature room for 24 hours prior to testing. The subjects were partially but incompletely acclimatized to the testing temperature by the summer weather and by the short periods of exposure to the higher temperatures of the room. In somewhat similar experiments, the effects of infusing serum albumin and of hemorrhage on performance ability in the heat were studied using 4 other men as subjects.

2. Removal of 500 cc. of blood (venesection) resulted in an immediate and marked decrease in ability to carry out physical activities (active and passive standing, exercising on bicycle ergometer) in the heat. Several days elapsed before control level of performance was attained again. Performance was affected adversely, but to a lesser degree, following removal of 200 cc. of blood. Subjects also performed poorly following confinement to bed and exposure to cold. Infusion of serum albumin in quantity equivalent to 500 cc. of blood plasma improved performance.

3. These various procedures also altered the level of hemoglobin concentration (increase in concentration following experiments on bed rest and exposure to cold; decrease following venesection and albumin infusion) and blood volume. Performance in these experiments correlates well with

estimated levels of blood volume, but there is not any consistent relationship between performance and hemoglobin concentration.

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# *A Study on the Mechanism of Nitrous Oxide Analgesia*

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THE ANALGESIC ACTION of nitrous oxide was first demonstrated quantitatively by Seevers, Bennett, Pohle and Reinardy (7), who studied, by means of a specially devised needle algesimeter, changes in pain threshold caused by this gas, as well as by cyclopropane and ether. The optimum concentration of N<sub>2</sub>O, with retention of ability to cooperate, was found to be 35 to 40 per cent. A later study by Chapman, Arrowood, and Beecher (1) revealed that 20 per cent N<sub>2</sub>O is as effective an analgesic as is 15 mgm. morphine sulfate, measured by the Hardy-Wolff-Goodell method (4) and by amelioration of muscle ischemia pain.

The present study was undertaken as an extension of the above work, with the aim of investigating *a*) the quantitative aspects of the analgesia and *b*) the relationship between the analgesia and general psychomotor performance. It was hoped that elucidation of the latter point, particularly, might give some insight into mechanisms of analgesia in general.

## METHODS

Eighteen young men served as subjects for the experiments. No special preparations were made for the tests with regard to eating, medication, etc. Pain threshold was determined by the method of electrical stimulation of the tooth pulp through a metal filling (2). Psychomotor activity was measured by means of the Johnson code test (5). This consists of different sets of nonsense words, with the respective letter codes; the sets are standardized so that each requires the same performance time in the trained subject. Most of the subjects were given one to three practice tests before the actual experiment so that the learning factor might be reduced. Some of the subjects, however, were given no preliminary tests so that in these cases only tests showing an increased performance time might be considered of significance. In all cases, nitrous oxide was administered with oxygen by nasal mask, with constant flow at atmospheric pressure from standard anesthesia

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equipment. The Millikan oximeter (6) was used to determine the level of oxygen saturation in a few cases.

At least three control pain threshold determinations were made after the mask was placed during administration of 100 per cent  $O_2$ . The subjects were not notified when administration of  $N_2O$  was begun, although most detected the gas by its odor. Threshold readings were made at one- or two-minute intervals until the effect was constant for at least three readings. At this time, either a psychomotor test was given while the gas was flowing at the previous concentration, or the concentration of  $N_2O$  was raised to a new level, or administration of the gas was stopped. An attempt was made to follow the threshold readings until they returned to the basal level, but this was not possible in all cases.

Every threshold reading consisted in the determination of the intensity of stimulus necessary to produce each of two sensory end-points in the tooth. The first of these was a just perceptible sensation, not painful in itself; the second was that point at which, with an increased stimulus, this sensation merged into true pain. The stimuli responsible for these two end-points are hereinafter referred to as *thresholds I* and *II*, respectively. This phenomenon of the double threshold, with the method employed, has been previously noted (3). The instrument was calibrated in steps of 0.2 volts, from 0.0 to 4.2 volts, and readings were interpolated to the nearest 0.05 volt.

## RESULTS

Control observations of the effect of 100 per cent  $O_2$  on pain threshold showed no difference over air inhalation with the mask in place. The control values ( $\bar{X}$ ) represent combined averages of the mean of three control readings at each test. Similarly, the values for increment of threshold ( $\bar{X}_0$ ) during inhalation are the combined averages of the mean of three readings, when the analgesic action was at its height. This was usually reached in three to six minutes after commencing administration of the gas.

Table 1 summarizes the results observed under  $N_2O$  inhalation at 10, 20, 33 and 40 per cent in  $O_2$ . It is seen that there is an increase of both thresholds over the entire range of  $N_2O$  concentration studied. There is no direct correlation of the absolute value of increase of the threshold with the concentration of  $N_2O$ , although there is a rough proportionality between the percentage increase and the concentration of gas, particularly with *threshold II*. The significance of the results on *threshold I*, as expressed by the *P* values, is variable, while there is uniformly high significance of the increments of *threshold II* at concentrations greater than 10 per cent. It was the general observation of the subjects that the influence of the gas caused a change in the 'quality' of the pain so that with increasing concentrations

of the gas it became increasingly difficult to denote the point at which the sensation became true pain. *The element of noxiousness of the stimulus was decreased*, and the sensation became somewhat more 'diffuse'.

The results of the Johnson code tests, table 2, show an increase in performance time which is roughly proportional to gas concentration from 10 to 33 per cent. Likewise, in this range the significance of the increment increases with increasing concentration. The disadvantage of such a small

TABLE 1. EFFECT OF NITROUS OXIDE ON THE TOOTH PAIN THRESHOLD

N <sub>2</sub> O	N	n	X	X <sub>D</sub>	s	s <sub>X<sub>D</sub></sub>	P
<i>Threshold I</i>							
%			<i>x</i>	<i>r</i>	<i>p</i>	<i>r</i>	
10	7	7	1.00	+ .20	.17	.064	.05-.02
20	12	15	1.00	+ .25	.19	.048	< .01
33	9	9	1.20	+ .25	.58	.192	.2
40	4	4	.90	+ .20	.27	.133	.3-.2
<i>Threshold II</i>							
10	7	7	1.95	+ .35	.43	.163	.1-.05
20	12	15	1.95	+ .45	.47	.121	< .01
33	10	13	1.05	+ .35	.35	.097	< .01
40	5	6	1.20	+ .30	.25	.103	.05-.02

N = Number of subjects. n = Number of trials. X = Mean control threshold reading, in volts. X<sub>D</sub> = Mean increase in threshold, in volts. s = Standard deviation. s<sub>X<sub>D</sub></sub> = Standard error. P = Probability for random selection, as determined from Fisher's 't-Table'.

number of tests as was performed at 40 per cent N<sub>2</sub>O is reflected in the low significance of the results. Of the tests in which the decoding time was not increased, two of the four at 20 per cent and one of the three at 10 per cent corresponded with an increase in pain threshold. There were no cases, however, in which the code test time increased without a simultaneous rise in the pain threshold.

Oximeter readings were made on four occasions during administration of 33 per cent N<sub>2</sub>O. These showed 95, 98, 100, and 100 per cent oxygen saturation of the blood, respectively. The findings were no different from control values on the same subjects under administration of 100 per cent oxygen.

#### DISCUSSION

This study corroborates previous reports (1, 7) to the effect that nitrous oxide has an analgesic action in concentrations below those necessary for surgical anesthesia. This effect is certainly present at 20 per cent, while 10

per cent appears to be a critical point where the pain threshold of some subjects is raised, while that of others is unaffected.

It is of interest to correlate the greater absolute increase in *threshold II* over *threshold I*, as well as the higher significance with the fact that end-point II became progressively more obscure with increase of  $N_2O$ . It is difficult to determine whether this phenomenon is due to a change in attitude towards the noxious stimulus or to a real effect on perception. The rise in *threshold I* indicates an effect on perception, whereas the qualitative change in the second end-point suggests a change in attitude or interpretation.

TABLE 2. EFFECT OF NITROUS OXIDE ON PERFORMANCE OF THE JOHNSON CODE TEST

$N_2O$	TOTAL TESTS	INCREASED TIME	DECREASED TIME	NO CHANGE ( $<5\%$ )	AVERAGE TIME CHANGE	P
%					%	
10	6	3	1	2	+9	.2
20	10	6	0	4	+16	.05-.02
33	5	5	0	0	+40	<.01
40	2	2	0	0	+20	.2

Despite the limitations of the code test as we have used it for measuring psychomotor activity, one can safely say that there is, with  $N_2O$  analgesia, a concomitant decrease in psychomotor performance. The results of the tests with 10 per cent  $N_2O$  are somewhat difficult to interpret accurately. Because it was difficult to control the learning factor, those tests which showed no change or a decrease in performance time are correspondingly of relatively little significance. Since only one of these three tests in question at 10 per cent  $N_2O$  was associated with an increased pain threshold, we must conclude that, at least in general, a rise in pain threshold is associated with decreased psychomotor performance.

Accordingly, it appears that the analgesic action of nitrous oxide is but one manifestation of a general central nervous system depression. That this is not due to relative anoxemia is demonstrated by the oximeter readings, as well as the fact that in all cases at least 60 per cent oxygen was being administered. This may well be the mechanism of the analgesia produced by other anesthetic gases.

#### SUMMARY

Nitrous oxide, when administered in concentrations of 10 to 40 per cent in oxygen, produces a rise in tooth pain threshold in the presence of an arterial oxygen saturation of 95 to 100 per cent. Psychomotor performance, as measured by the Johnson code test, decreases under administration of



nitrous oxide in concentration of 10 to 40 per cent in oxygen. It is concluded that the analgesia produced by nitrous oxide is associated with and is most probably a manifestation of general central nervous system depression.

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# *Absolute Muscle Power and Ischemic Work Ability of Muscle*

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IT IS EVIDENT from published data (1-9) that individuals differ in their abilities to perform ischemic work. Furthermore, ischemic work ability differs even in the two arms of the same subject (4, 5), with pain appearing earlier in the left arm in right-handed subjects.

In the experiments of LaPlace and Crane (5), no female subject developed intolerable pain and a majority of the elderly males terminated the exercise because of fatigue. The probable explanation given is that relative muscular weakness prevented their exercising to the point at which intolerable pain developed.

The difference in the two arms, according to Katz *et al.* (4), is associated with training, since the right hand had been clenched much more frequently than the left in all of their subjects.

Training was found by Maison and Broeker (8) to produce small and slow gains in total work done by ischemic muscle. In a 16-month period of training, there was a maximum increase of only 30 per cent in total work done by the ischemic muscle, although the intensity of the ischemic pain was markedly reduced during the period of training. These investigators failed to test the absolute power of the muscles in an early stage of the experiments, but they did make these determinations near the end of the training period. The results of the tests led them to suggest that absolute muscle power and ischemic work ability are unrelated, and that they may depend upon different processes in muscle.

Differences in ischemic work ability in the two arms of the same subject (4, 5), and the failure of females and most elderly males to develop intolerable pain during ischemic exercise (5), suggest the possibility that the strength of muscle and ischemic work ability may be related. Since Maison and Broeker (8) have investigated this relationship in only a few subjects, and that after a prolonged period of training, the present experiments were undertaken in an effort to determine the degree of correlation between absolute muscle power and ischemic work ability in subjects trained just long enough to give consistent results.

## METHODS

Thirty-three subjects, 22 male and 8 female students ranging in age from 20 to 28 years, and 3 males, 35 to 40 years of age, without evidence of peripheral vascular disease, were used in the studies. The method of study was adapted from that of Harrison and Bigelow (3). With the subject

seated, the right arm was rested upon a support above his head. A sphygmomanometer cuff, which encircled the upper arm, was rapidly inflated to 250 mm. Hg. After lowering the arm to a horizontal support, the fingers were flexed once per second against a gripping device with a load of 1.1 kgm. The subject announced the appearance of a minimal pain sensation in the forearm or hand, then a definite sensation of pain, and finally intolerable pain. The duration of exercise to each of these points was recorded in seconds by a stopwatch out of the subject's range of vision. A single daily test, at approximately the same hour, was made upon each subject.

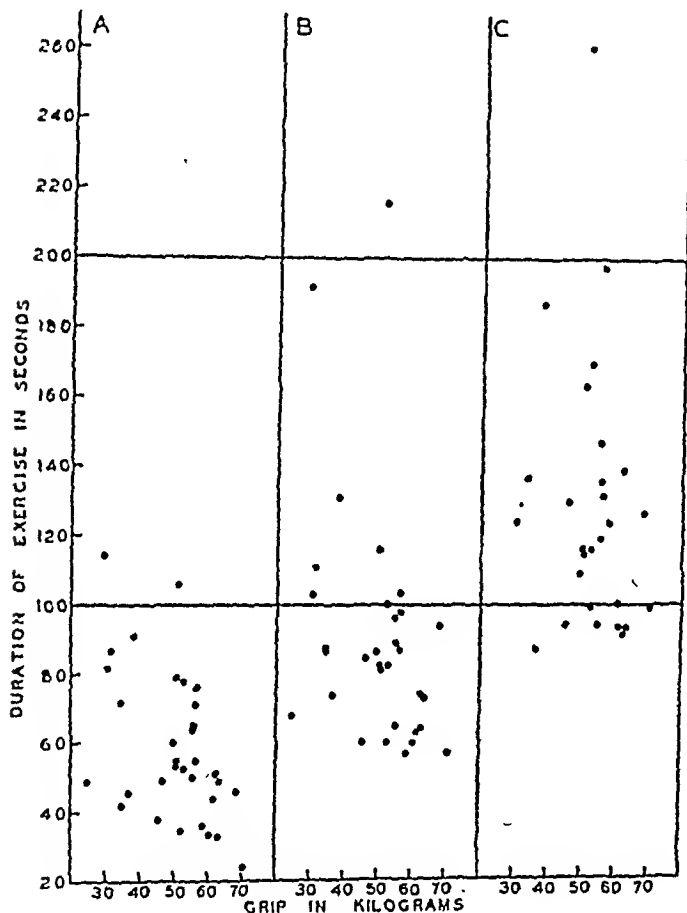


Fig. 1. RELATION OF DURATION of ischemic exercise in seconds to the point of minimal pain, A; definite pain, B; intolerable pain, C; to grip in kilograms. Each point represents the mean of the 3-day experimental period in a single subject.

As the index of absolute muscle power, grip was measured with a Smedley-type dynamometer, graduated in kilograms and fitted to the hand with an adjustable inside stirrup. The dynamometer was calibrated by suspending known weights from the stirrup throughout the range of the instrument. In each test, the dynamometer was gripped three times with the maximum effort being recorded.

Daily determinations of ischemic work ability and grip were continued until the subject had demonstrated familiarity with the procedures, as indicated by consistent results. When this state was reached, usually within

one week, the results of the three tests immediately following were utilized in the study. Subjects were not informed of the details of the study in progress.

### RESULTS AND DISCUSSION

In figure 1 the duration of ischemic exercise, in seconds, to the points of minimal pain (A), definite pain (B) and intolerable pain (C) is plotted against grip in kilograms. Each value represents the mean of the results obtained on the three experimental days. The marked degree of scatter in each group is clearly evident. The coefficients of correlation with their probable errors are  $-0.423 \pm 0.056$ ,  $0.236 \pm 0.060$  and  $-0.052 \pm 0.001$ , respectively, thus indicating an insignificant degree of correlation between ischemic work ability and grip. These findings lend support to the suggestion of Maison and Broeker (8) that anerobic work capacity and absolute power may depend upon different processes in muscle.

In each individual the values of the daily determination of grip over the three-day period were recorded, with the mean being plotted as indicated above. The constancy of repeated determinations of grip in the same individual was indicated by averaging the three daily values and then calculating the percentage deviation of each day's value from the mean. In the 33 subjects, the percentage deviations of the various subjects ranged from 0.0 to  $\pm 5.5$ , with a mean average of  $\pm 1.8$  for the entire group.

The duration of ischemic exercise to each of the three points was more variable than the grip. The individual durations to the point of minimal pain were averaged for the three-day period. The percentage deviation of each day's duration from that subject's three-day mean was calculated. The individual percentage deviations ranged between  $\pm 1.5$  and  $\pm 17.5$ , with the mean average of all 33 subjects being  $\pm 7.6$ . To the point of definite pain, the individual range of percentage deviations was from  $\pm 0.5$  to  $\pm 11.5$ , with a mean average of  $\pm 4.1$  for the entire group; to the point of intolerable pain, individual percentage deviations ranged from 0.0 to  $\pm 10.0$ , with a mean average of  $\pm 4.3$  for the entire group. The points of definite and intolerable pain show approximately the same degree of constancy with both being less variable than the point of minimal pain.

The results of the study revealed no greater degree of correlation between duration of ischemic exercise and grip in males than in females. The eight females exhibited weaker grips than any of the males, yet their capacities for ischemic work showed the same marked variability and fell within the ranges noted in the males. Unfortunately, four of the female subjects did not exercise to the point of intolerable pain, but the four that did proceed to this point gave results closely similar to those obtained in the males. The

appearance of intolerable pain in these female subjects is in contrast to the finding of LaPlace and Crane (5) that no female subject developed intolerable pain. In our series intolerable pain developed in the females after 87, 124, 137 and 187 seconds, respectively, using a load of 1.1 kgm. In the series of LaPlace and Crane, using a 10.0 kgm. load, fatigue terminated the exercise in 23 to 78 seconds. The latter individuals probably would have experienced intolerable pain had they been able to continue the exercise for a longer period of time.

#### SUMMARY

In 33 subjects, including 8 females, who were trained only long enough to give consistent results, there was no significant degree of correlation between ischemic work ability and absolute muscle power, using grip as the index of the latter. It is concluded that ischemic work ability and absolute muscle power are unrelated and probably depend upon different processes in muscle.

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## *Vagotomy and the Hunger-producing Action of Insulin in Man*

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THE STIMULATION OF 'HUNGER' by insulin is well known. The usual explanation (1) of the mechanism of this effect is that the insulin induces hypoglycemia, which, in turn, acts as a stimulus to the vagal centers leading to augmentation of gastric motor activity. The augmented gastric contractions are believed to give rise to the sensation of hunger.

Recent studies on animals have cast doubt on the adequacy of this explanation. Morgan (2), working with rats, and Grossman and co-workers (3), using dogs, have demonstrated that complete bilateral vagotomy, which is known to abolish the gastric motor response to insulin hypoglycemia, does not prevent or even impair the augmentation of food intake produced by insulin.

It is reasonable to assume that the increase in food intake in these animals indicated that the insulin still gave rise to hunger sensations after vagotomy. However, a direct answer to questions about sensations can only be obtained by studies in man. The current use of the operation of complete bilateral vagotomy in the treatment of peptic ulcer afforded us a number of subjects in whom we could seek an answer to the question: Does insulin induce sensations of hunger in the human subject after complete vagotomy? This report is concerned with our studies directed toward an answer to this question.

In the course of these studies, it became apparent to us that the usually accepted concepts of hunger could not be well fitted to our observations.

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The reformulation of these concepts will be discussed after the presentation of our results.

### METHODS

These studies were performed on a group of 23 patients who underwent the operation of bilateral vagotomy for the treatment of peptic ulcer. The operations were performed on the Surgical Service of Dr. Karl A. Meyer at the Cook County Hospital. The clinical, physiological and pharmacological aspects of vagotomy in this group of patients have been presented elsewhere (4-7). The observations reported here were made incidentally while performing the insulin test on these patients in order to determine whether or not the vagotomy was complete. During the insulin test observations on both gastric secretion and gastric contractions were made. The technique has been described (4). Essentially, it consists of the intravenous administration of 15 units of crystalline insulin after a 15-hour fast. Two gastric tubes were in place, one for removal of secretions, the other having a balloon attached and connected with a water manometer for recording gastric contractions.

Only patients in whom the insulin test (4) indicated that vagotomy was complete are included in the tabulated results. In most instances one insulin test was performed during the week before operation and one test during the second week after the operation. In five patients, only the postoperative test was performed; in one instance this was done three months after the operation. In two other patients tests were performed four and five months postoperatively in addition to the test shortly after the operation.

In addition to the observations on gastric secretion and motility, data were also collected on the sensations which the patient experienced and the occurrence of general manifestations of insulin hypoglycemia such as sweating.

In obtaining the information from the patient, leading questions were avoided. For instance, the patient was never asked, "Are you hungry?" but merely, "How do you feel?"

### OBSERVATIONS

*Latent Period.* When hunger occurred following insulin injection, it usually began after the depth of the hypoglycemia was passed. It never occurred sooner than 30 minutes after the insulin injection and usually required about 45 minutes to appear. When a gastric secretory response was present (prevagotomy studies), it usually began before hunger was reported.

*Duration.* The hunger sensation usually lasted until food was given at the termination of the test, which usually was one and one-half to two hours after the insulin injection. Occasionally it lasted for a shorter period, subsiding spontaneously.

*Incidence of Hunger Reaction and the Effect of Vagotomy.* Hunger was reported during the insulin test by 12 of 18 patients before vagotomy and by 20 of 23 patients after the operation. In 4 patients hunger did not occur during the preoperative test but did in the postoperative test. The results are summarized in table 1.

*Character of Hunger Sensations, Correlation with Gastric Contractions and effect of Vagotomy on Each of These.* When the patients were asked to describe their hunger sensations they usually were somewhat at a loss. Most frequently they stated that they had a sensation of emptiness. This was not localized to the epigastrium, but usually was diffusely localized to the entire abdomen. Often the patients were unwilling to localize the sensation of hunger and said that they "felt hungry all over." In addition, most of the patients complained of a sensation of weakness. Both the sensation of weakness and that of emptiness were associated with a desire for food. Motility tests were made on 15 of the patients preoperatively and gastric contractions were observed in each instance, both spontaneously and following insulin hypoglycemia. Twenty-five motility tests were made on 23 patients postoperatively. Contractions did not occur in any of these tests either spontaneously or after insulin hypoglycemia. This absence of contractions generally associated with hunger is consistently found in patients who show a negative secretory response to insulin hypoglycemia, indicating a physiologically complete vagotomy (4).

Before vagotomy we could elicit a report of the typical epigastric pang of distress associated with the individual gastric contractions in only four patients. In two of these instances, the wave of gastric contraction was associated with distress which the patient designated as ulcer pain. In all four instances the gastric contractions and the sensations that occurred synchronously with them were abolished by vagotomy. However, these patients continued to feel hungry, both spontaneously and as a result of insulin injection. The only difference they recognized was that after vagotomy one component of the complex set of sensations associated with hunger was absent.

Most of the patients did not recognize any alteration in the character of their hunger sensations as a result of vagotomy. In these patients even intense hunger sensations failed to be correlated with gastric motor activity before vagotomy and were unaltered by the absence of motor activity caused by vagotomy.

#### DISCUSSION

These studies in man confirm the impression gained from studies on animals which indicated that the augmentation of hunger produced by insulin is independent on the effect on gastric motor activity. A proper discussion of these findings cannot proceed without an examination of the current concepts of hunger.

The most widely accepted definition of hunger is that of Carlson<sup>1</sup> (8, p. 6). He defines hunger as "a more or less uncomfortable feeling of tension or



pressure and pain referred to the region of the stomach". He goes on to show, in confirmation of Cannon and Washburne (9), that these epigastric hunger pangs are synchronous with and are caused by the contractions of the empty stomach. This observation has been repeatedly confirmed and is supported by the findings of the present studies. However, several important questions arise in regard to this phenomenon: *a)* How frequently do hunger pangs correlated with gastric contractions occur as a part of the hunger sensation complex? *b)* What relationship do these hunger pangs have to the other sensations associated with hunger?

Carlson (8, p. 84) states: "Many apparently normal persons experience in hunger, besides the gnawing pressure-pain sensation in the stomach, a feeling of weakness, 'emptiness', headache and sometimes even nausea . . . . We call these states or symptoms accessory hunger phenomena, because they are not always present in hunger and because their relative preponderance depends on the length of starvation and on some individual peculiarity in the person. It must be admitted, however, that in some individuals these accessory hunger phenomena appear to overshadow, if not entirely to suppress, the pressure-pain sensations from the stomach".

"The weakness accompanying hunger is evidently of complex origin, or partly due to sensory impulses from the digestive tract, and partly to relative exhaustion in the tissues. . . . That in moderate hunger only the first or reflex factor is involved is evident from the fact that this weakness is abolished by taking food into the stomach before there is any digestion and absorption of the food material into the blood" (p. 92).

"Strong sensation of hunger is usually accompanied by a peculiar feeling of 'emptiness' in the entire abdominal region. This feeling is continuous, not intermittent like the pangs of hunger. . . . It is probable that the increased tonus of the abdominal muscles, in consequence of the empty state of the stomach and intestines, contributes to the feeling in some way" (p. 93).

Finally, he concludes (p. 94): "So far as established facts permit conclusions or point the way, the accessory hunger phenomena, excepting the exhaustion fatigue of prolonged starvation, are caused reflexly by the hunger tonus and the hunger contractions of the empty stomach."

In other words, Carlson takes the position that the dominant feature of hunger sensations is the pang associated with the contraction of the empty stomach. The other sensations occurring in hunger, which he terms accessory hunger phenomena, are considered by him to be of secondary importance and, for the most part, to be caused by the hunger contractions. The results of the present study indicate that these so-called accessory phenomena are more frequently present and more prominent than the epigastric pang associated with contractions, and persist unaltered after the hunger pangs have been abolished by vagotomy.

Our findings are at variance with the conclusion of Quigley (1) and co-workers, who studied gastric motility and hunger sensations after insulin in man. They stated: "Since there was usually complete agreement be-

tween gastric motility and hunger sensations, our experiments support the contention that hunger sensations are of peripheral origin and are the direct result of the gastric movements."

The hunger sensations associated with the contractions of the empty stomach, namely the hunger pangs, are caused by the stimuli which these contractions produce. For this reason, this part of the hunger sensation

TABLE 1. OCCURRENCE OF HUNGER SENSATIONS AND OF GASTRIC CONTRACTIONS IN RESPONSE TO INSULIN HYPOGLYCEMIA BEFORE AND AFTER COMPLETE VAGOTOMY

PATIENTS	BEFORE VAGOTOMY				AFTER VAGOTOMY			
	Hunger			Contractions	Hunger			Con- tractions
	Severe	Moderate	None		Severe	Moderate	None	
FS.....	not tested pre-op.						x	o
MP.....			x	not done	x			o
TT.....			x	+			x	o
PF.....			x	+	x			o
MA.....			x	not done		x		o
AW (9 mos. after).....	not tested pre-op.					x		o
TS.....	x			+	x			o
LB.....			x	+		x		o
FR.....			x	+ <sup>1</sup>	x			o
AB.....	x			+ <sup>2</sup>	x			o
JG.....	x			+ <sup>2</sup>	x			o
JC.....	x			+ <sup>3</sup>		x		o
OS.....	x			+ <sup>3</sup>	x			o
ET.....	x			+		x		o
RB.....		x		+		x		o
HP.....	not tested pre-op.			-	x <sup>4</sup>			o
JV.....	x			+ <sup>5</sup>	x			o
RK (3 mos. after).....	not tested pre-op.			-	x			o
ND.....	not tested pre-op.					x		o
SB.....	x			not done		x		o
SB (5 mos. after).....	repeat post-op. test				x			o
OB.....	x			+ <sup>2</sup>		x		o
OB (4 mos. after).....	repeat post-op. test				x			o
MR.....		x		+ <sup>5</sup>		x <sup>4</sup>		o
EH.....		x		+ <sup>5</sup>		x <sup>4</sup>		o
23 patients.....	9	3	6		12	11	2	
18 pre-op. tests.....								
25 post-op. tests.....								

<sup>1</sup> Contractions caused ulcer pain.

<sup>2</sup> Hunger occurred during both periods of motility and periods of quiescence.

<sup>3</sup> Hunger occurred during period when contractions were absent.

<sup>4</sup> Recognized change in character of hunger, from gnawing to empty.

<sup>5</sup> Contractions caused ulcer pain, hunger occurred during period of absent motility.

Recognized each contraction as a hunger pang.

complex is referred to as being of 'peripheral' origin. The origin and nature of the stimuli for the nonlocalizable diffuse aspect of the hunger sensation is not known. However, because of this diffuseness it has been suggested that this sensation is of 'central' origin (11). The theoretically possible sources of the stimuli for the diffuse element in hunger are numerous. For instance it may involve nervous impulses coming from many tissues or it may be due to a change in the composition of the blood or to the addition of a hormonal substance to the blood. Until more is known about the origin of these stimuli, clarity can probably best be attained by referring to gastric and extra-gastric factors in hunger sensations.

The objection may be raised that the type of sensations elicited by insulin is not similar to those which occur spontaneously during hunger. This point requires an objective answer by careful study of many normal human subjects. Our own experience and information gained from the interrogation of others indicate that our findings with insulin are representative of normal hunger sensations.

How does vagotomy abolish the hunger pangs associated with gastric contractions? As we have pointed out above, in those patients who recognized individual gastric contractions as hunger pangs, these sensations were abolished by vagotomy. Theoretically, this might be due either to the severing of the sensory pathway from the stomach or to abolition of the hunger contractions. We have found only one author who makes a statement about the afferent pathway for the hunger pang. Carlson (8, p. 214) says: "The vagi nerves are the main, if not the only, afferent pathway for the gastric hunger impulses." This conclusion is apparently based on the work of Miller (10), who claimed that no central reflexes of any kind can be evoked by stimulation of the stomach after section of all the vagus fibers to that organ.

Actually, the question of the afferent pathway for the hunger pang associated with gastric contractions is now susceptible to direct study in human beings, using patients who have undergone vagotomy as well as patients who have been subjected to sympathectomy.

Elsewhere (4) it has been reported that these completely vagotomized patients included in this study showed a complete absence of both spontaneous and insulin-induced gastric hunger contractions. Therefore, the disappearance of the hunger pangs in these patients can be accounted for on the basis of the absence of the contractions which produce them. Of course, it is possible that vagotomy also severed the sensory pathway, but this cannot be proved or disproved in the absence of contractions.

We have had the opportunity to study the occurrence of hunger pangs in two patients<sup>2</sup> before and after bilateral sympathectomy for the treat-

<sup>2</sup> These studies were conducted by Dr. M. Zweig of the Cook County Hospital.

ment of hypertension. Both of these patients recognized each contraction as a sensation of epigastric distress before the operation. After the operation, the contractions occurred with about the same vigor and frequency as preoperatively, but they no longer produced distress. This clearly indicates that the splanchnic nerves are the afferent pathways for the distress associated with gastric hunger contractions and that no such pathways exist in the vagus nerves.

Thus, both vagotomy and sympathectomy abolish hunger pangs, the former by depressing gastric motor activity and the latter by interrupting the sensory path.

#### SUMMARY

The sensations of hunger induced by insulin continue to occur after complete vagotomy in man. These sensations include feelings of emptiness and weakness. In those persons in whom epigastric pangs of distress associated with individual gastric contractions are a part of the sensation complex of hunger, vagotomy, by abolishing the contractions, eliminates this particular kind of sensation. The removal of this component of the sensation-complex of hunger is recognized by the subject, but it does not cause a significant change in the general affective response to hunger.

In most of the subjects, the gastric component of the hunger sensations is absent or negligible both before and after vagotomy. In these subjects, vagotomy caused no detectable change in the hunger response to insulin.

Both gastric and extra-gastric stimuli contribute to hunger sensations in man. In most individuals, the extra-gastric components predominate in the sensation-complex of hunger. Elimination by vagotomy of the gastric component of the hunger sensation complex (hunger pangs) has no significant effect on the manifestations of the extra-gastric components (feelings of weakness and emptiness associated with the desire for food). Vagotomy abolishes the gastric hunger pang by abolishing the gastric hunger contractions, not by interrupting the sensory pathway.

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# *Effect of Meals on Visual Performance and Fatigue<sup>1</sup>*

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HAGGARD AND GREENBERG (1) have reported favorable effects of in-between meal feeding on fatigue and stressed several conclusions: *a*) the beneficial effect is dependent on carbohydrate, *b*) increased carbohydrate utilization produces an increased mechanical efficiency of work and *c*) these effects are reflected in increased work output in light industry. Recording the average hourly performance in sewing tennis shoe tops, Haggard and Greenberg (1) reported that the output rose with the number of meals taken per day as these were increased from two to five per day.

The idea that frequent feeding is desirable is supported indirectly by the study of Clarke, De Jongh and Jokl (2) when it appeared that athletic performance of Moslem school children is poorer during the Ramadan month when only two meals a day are eaten. However, the studies of Haggard and his colleagues are technically imperfect because of the lack of controls and the limited time periods used in the measurement of energy expenditure.

Haggard and Greenberg's main finding is the continuous drop of the blood sugar, R.Q. and mechanical efficiency from a peak in the morning after breakfast towards noon, and a rise after lunch to a value comparable to the morning peak. While some effect of carbohydrate utilization on mechanical efficiency has been known since the work of Krogh and Lindhard (3), Haggard and Greenberg's claim of an increase of the mechanical efficiency of 25 per cent is far out of line with all other observations (4-7). Also, changes of the R.Q. and of the blood sugar are frequently not parallel (4).

Haldi and Wynn (8) made more precise experiments with high and low carbohydrate meals of 1050 Cal. and found the latter produced greater carbohydrate utilization but had no advantage for endurance or mechanical efficiency. The same authors (9) were unable to discern any improvement from carbohydrate ingestion in brief strenuous performance (swimming).

Obviously, there are several separate but related questions: 1) Is total work performance at nonstrenuous tasks raised by between-meal feeding? 2) Is the nutrient character of the meal consequential in this respect? 3) If the feeding is beneficial, what is the mechanism of its action?

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The available evidence on these points is inadequate, particularly in view of the large practical applications. The present paper is a report on an experimental study of the effects of meals in a miniature job situation which demands constant attention and which produces fatigue but involves little expenditure of energy.

#### METHOD

A controlled work task was developed in this laboratory for the study of visual performance and fatigue (10). It represents the essential features of an inspection job on a conveyor belt. The work task was subjectively felt as strenuous and produced objective visual fatigue during a period of two hours. A battery of tests was applied before and after the work task, and significant fatigue trends of visual functions were observed (11) which could well be used for the study of the effect of meals.

The visual task, described in detail elsewhere (10), consisted in the recognition of small letters, which were presented in random order behind a narrow slit. The total size of the letters corresponded to a visual angle of 10 minutes. The exposure time from the first appearance of the letter in the slit to complete disappearance was 0.56 sec. The subjects copied the letters by hand on a band of paper, led underneath a metal plate containing a small window for writing down the letters, and transported by depressing a lever with the left hand. The writing of the letters and the transport of the paper was done without visual control and did not require any appreciable skill. In order to increase the severity of the visual stress, the illumination on the screen was adjusted to a level of 5-foot candles, which is inadequate for this strenuous task (11). As illuminants Verd-A-Ray bulbs were used. This illuminant has a greenish coating, but the light emitted is essentially white (12). The 6 subjects were seated in individual booths.

The work task was performed continuously for two hours and was evaluated in terms of the number of letters correctly recognized out of a sample of 200 letters; this corresponded to a time interval of six minutes. Three such work samples were evaluated. The first sample was taken beginning five minutes after the start of the work, a second sample at the mid-point (after 1 hour of work), and the third sample near the end. The subjects had the impression that the whole two-hour performance was evaluated.

The average of the three samples gives the 'average performance score'. In addition, the difference between the first and the third sample ('performance drop') and the difference between the highest and lowest value of the three samples ('performance range') was calculated. The latter is an index of the maximal intra-individual variability during the work test.

### Visual Functions Tested

The *blinking rate* was measured for periods of 5 minutes at the start, midpoint and end of work. The results were expressed as 'average blinking rate per minute' (means of the three periods) and 'blinking rate difference' (change from the first to the last period).

A battery of visual tests was applied immediately before and after the work; three groups of test items were spaced at intervals of about 5 minutes in the following order: *a*) Recognition time for dots of threshold

TABLE 1. UNITS OF FUNCTIONS AND THE 'DESIRABLE' VALUES OF THE SCORES

Retinal Functions	UNITS	'DESIRABLE' VALUES
Recognition time	Seconds	Lower
Flicker Fusion Frequency	Flashes per second	Higher
Brightness Discrimination, green	Arbitrary Units	Lower
Brightness Discrimination, red	Arbitrary Units	Lower
<i>Ophthalmological Tests</i>		
Abduction	Diopters	Higher
Adduction	Diopters	Higher
Vertical Divergence	Diopters	Higher
Accommodation near point	Centimeters	Lower
Convergence near point	Centimeters	Lower
<i>Performance Criteria</i>		
Performance average	No. of correct letters	Higher
Performance drop	No. of correct letters	Lower
Performance range	No. of correct letters	Lower
<i>Blinking Rate</i>		
Blinking rate average	Blinks per minute	Lower
Blinking rate difference start-finish	Blinks per minute	Lower
Questionnaire Score	Arbitrary Units	Lower

size and fusion frequency of flicker (f.f.f.); *b*) abduction power, adduction power, vertical divergence, accommodation near point and convergence near point; *c*) brightness discrimination (red and green).

*Recognition time for stimuli of threshold size.* The visual acuity was determined by means of small black dots of varying size, inserted in white paper squares, pasted on a disk and presented through a window 1.5 x 2.5 inches. The time from the start of the exposure to recognition was measured by means of a stop watch, and the value for the smallest dot which could be seen was used as the 'recognition time'.

*Fusion frequency of flicker (f.f.f.).* The rate of flashes was automatically increased starting from coarse flicker. At the moment of fusion, indicated by the subject through an acoustic signal, the rate of flashes per second was read on a scale.

*Abduction power, adduction power, vertical divergence, accommodation and convergence near point.* Routine ophthalmological procedure was used, described in detail elsewhere (11). All readings were made in triplicate and averaged. Abduction power, adduction power and vertical divergence

are expressed in terms of prism diopters at the point of diplopia. The accommodation near point is expressed as distance of the point of blurring from the intra-orbital bony rim in cm., and the convergence near point as the distance in cm. of the point of diplopia from the bridge of the nose. Except for the convergence near point, which involved both eyes, all measurements were made in the dominant eye.

*Brightness discrimination.* The Pulfrich photometer was used for this test. The left half of the visual field was set at a standard brightness level. The right half of the visual field was set at zero level (darkness), and the subject was asked to increase the brightness, by turning a knob, until both halves matched. No correction was permitted for overshooting, but the reading was repeated. The accuracy of matching was determined

TABLE 2. MEAN VALUES ( $\bar{M}$ ) AND FATIGUE CHANGES ( $\bar{d}$ ) OF PERFORMANCE, BLINKING RATE AND QUESTIONNAIRE SCORE AT FOUR VARIATIONS OF MEAL INTAKE.

STATISTICAL SIGNIFICANCE EXPRESSED BY THE F-TEST

Averages of 12 observations

FUNCTION	TYPE OF MEAL							
	No meal		Standard		Fat		CHO	
	mean ( $\bar{M}$ )		mean ( $\bar{M}$ )		mean ( $\bar{M}$ )		mean ( $\bar{M}$ )	
Performance average.....	167.0		173.4		171.3		162.4	
Performance range.....	24.7		18.2		19.5		25.7	
Blinking rate av.....	13.2		10.6		11.2		10.9	
	$\bar{d}$	F	$\bar{d}$	F	$\bar{d}$	F	$\bar{d}$	F
Performance drop.. ....	-16.9	6.64*	-14.9	10.69†	-10.9	9.84*	-3.9	0.23
Blinking rate diff.....	-1.7	3.00	+1.2	0.36	-0.8	0.59	+0.4	0.03
Questionnaire score.....	12.2	34.75†	9.1	54.88†	9.6	25.11†	6.7	7.83

F\* = 5.12 at the 5 per cent level, F† = 10.56 at the 1 per cent level of significance.

in arbitrary units, as the difference between the true brightness of the right and the left halves. Five repeat measurements were made and averaged. The brightness discrimination was investigated first with green and then with red filters.

*Discomfort questionnaire.* After completing the brightness discrimination test, the subjects recorded their subjective responses in each experimental session by means of a standardized questionnaire containing 10 discomfort items. The items were rated on a 5-point scale, ranging from '0' (absent) to '4' (extreme). The score was calculated as the added sum of the 10 items.

In some of the functions measured an increase in the score would indicate deterioration (for instance recognition time for threshold stimuli, accommodation near point), in others, an improvement (work output, flicker fusion frequency). For reasons of a uniform presentation of the material and a better visualization of the trend of the results, the improve-



ment in all functions is indicated by '+', and the deterioration by '-'. Table I shows what direction of change in the original readings would correspond to an improvement, i.e., could be classified as desirable change.

In all functions, except average performance score and average blinking rate, we are concerned with the differences ( $d$ ) before and after the visual task, or at the beginning and at the end. Therefore, for the purpose of condensation, only the mean differences ( $\bar{d}$ ), and not the absolute figures, are given in the tables. The differences between the  $\bar{d}$  after different meals are designated as  $\bar{\Delta}$ .

*Subjects.* The subjects were 6 young men (ages 20 to 29) who had served in the Laboratory for the year preceding the research on visual fatigue as full-time experimental subjects in nutritional investigations. They were physically normal, intelligent and cooperative, well accustomed and adjusted to the routine of laboratory work and testing. Their diet and daily routine and work were known, and any major interference from personal habits or accidental stresses could be excluded for the three months of visual experiments. Before the start of these studies, the visual characteristics of the subjects were thoroughly investigated and found to be within normal limits. The examination was repeated at the end of the testing period, in order to investigate whether three months of frequently repeated strenuous work would produce any detectable ocular changes. The individual ophthalmological data were given elsewhere (11).

### CONDITIONS

*Meals and procedure.* The work started 30 minutes after the meal (lunch), at about 1 P.M. A light breakfast was taken at 8 A.M. The following meals were compared: a 'standard' (balanced) meal, a 'high fat' meal, a 'high carbohydrate' (CHO) meal, and no meal.

The average composition of the standard meal was: carbohydrate calories 50 per cent, protein calories 12 per cent, and fat calories 38 per cent, totalling about 1300 calories. In the high fat meal, the fat calories were increased to 83 per cent and the carbohydrate and protein calories were decreased to 14 and 3 per cent, respectively, while the total calorie content increased slightly to 1400 calories. In the high carbohydrate meal, the percentage of carbohydrate calories was increased to 80, with 10 per cent protein and 10 per cent fat calories, and a total of about 1300 calories.

Duplicate series were made with each of these four variations of meals (including no meals), so that for each variation 12 values are available. The statistical comparison was made by means of the F-test.

The actual experiments started after a training period; a trend analysis was made (10), which proved the absence of any training trends when the

present series was started. The experiments were performed in an air-conditioned suite, at moderate room temperature.

### RESULTS

Table 2 shows the effect of meals on the performance criteria, blinking rate and discomfort questionnaire score. Surprisingly enough, the average performance was lowest and the performance variability (performance

TABLE 3. EFFECT OF MEALS ON FATIGUE CHANGES ( $\bar{d}$ ) OF RETINA FUNCTIONS. STATISTICAL SIGNIFICANCE EXPRESSED BY THE F-TEST

FUNCTION	TYPE OF MEAL							
	No meal		Standard		Fat		CHO	
	$\bar{d}$	F	$\bar{d}$	F	$\bar{d}$	F	$\bar{d}$	F
Recognition time.....	-4.25	3.54	-1.05	0.35	-0.45	0.08	0.75	0.16
Flicker fusion freq.....	-1.85	21.35†	-0.34	0.90	-1.08	6.62*	1.08	5.71*
Brightness discr. green.....	+0.14	0.33	+0.38	4.17	+0.04	0.01	+0.22	0.24
Brightness discr. red.....	+0.14	0.38	-0.31	1.17	-0.13	0.04	+0.07	0.04

F\* = 5.12 at the 5 per cent level, F† = 10.56 at the 1 per cent level of significance.

range) was highest after the high carbohydrate (CHO) meal, while the performance drop was smallest, but this might be due to the lower average level of the performance after the CHO meal. On the other hand, the discomfort (subjective fatigue) was least pronounced after the CHO meal and most pronounced when no meal was given.

Of the retinal functions (table 3), only the flicker fusion frequency (f.f.f.) showed any significant fatigue changes, most pronounced without meal, least pronounced after the standard meal. In contrast to previous results (11), the changes of the recognition time for threshold size were not significant, probably due to the smaller number of observations for each variation and to the choice of the illuminant. Fatigue changes of the f.f.f. and the recognition time for details were least pronounced with Verd-A-Ray lamps (12).

The extrinsic eye muscle functions (abduction and adduction power, vertical divergence, convergence near point, table 4) showed consistently the most significant deterioration after the CHO meal, while lens accommodation improved.

The statistical significance of the differences between meals ( $\bar{\Delta}$ ) in performance and trends of visual functions was calculated for most combinations, but for the purpose of condensation only the statistically significant differences are shown in table 5.

The greater deterioration of the average performance and performance range after the high carbohydrate meals is statistically significant, while

the smaller drop in performance was not significant (otherwise it would have been listed in table 5).

Also, the greater deterioration of extrinsic eye muscle functions after the CHO rich meal is statistically significant. On the other hand, the deterioration of the discomfort score and retinal functions was significantly greater when no meal was given. That the missing of lunch has an adverse affect on the subjective sensation of discomfort might have been expected, but objectively this was not associated with the greatest deterioration in most visual functions, in fact, in two functions (adduction power, accommodation near point), the deterioration was least pronounced.

TABLE 4. EFFECT OF MEALS ON FATIGUE CHANGES OF OPHTHALMOLOGICAL ROUTINE TESTS. STATISTICAL SIGNIFICANCE EXPRESSED BY THE F-TEST  
Average values of 12 observations

FUNCTION	TYPE OF MEAL							
	No meal		Standard		Fat		CHO	
	$\bar{d}$	F	$\bar{d}$	F	$\bar{d}$	F	$\bar{d}$	F
Abduct. power.....	-0.10	0.28	+0.08	0.07	+0.26	3.61	0.12	1.48
Adduct. power.....	+2.73	3.02	+0.36	0.13	+0.74	1.13	-2.96	9.62*
Vert. divergence.....	-0.20	1.73	-0.12	0.86	+0.08	2.08	-0.17	8.10*
Accom. near pt.....	+1.33	8.30*	-0.51	2.09	+0.23	0.53	+1.14	8.40*
Converg. near pt.....	-0.63	20.53†	-0.44	2.11	+0.15	0.02	-0.46	11.44†

F\* = 5.12 at the 5 per cent level, F† = 10.56 at the 1 per cent level of significance.

#### DISCUSSION

Visual performance is a complex integral involving a large number of physiologically different functions.

One can hardly expect that a certain type of meal would be optimum for all functions, and this is brought out by the results. For instance, after the CHO meal the performance criteria are poorest, but the subjective discomfort is least pronounced. In other words, it is impossible to state that a certain type of meal is the best for performance and fatigue in strenuous visual work. Although this is not surprising, it has not been demonstrated before, and some generalization on the effect of meals on industrial performance might be possible. Most types of industrial performance involve a great variety of physiological functions.

Our results do not show any evidence for a superiority of high carbohydrate meals, such as has been claimed for other types of work by Haggard and Greenberg (1). In fact, if anything, the CHO meals are inferior in regard to most items listed in table 5, including average performance and performance variability (range). It seems that the standard meal or the high fat meal are preferable for the majority of visual functions. The inferiority of CHO meals might be due, in part, to their greater bulk, but this does not change the differentiation so far as the composition of a lunch

is concerned. The results might have been different after concentrated carbohydrates such as candies.

It is of interest that all ophthalmological routine tests (table 4) show a significant differentiation between meals, although, in a previous investigation (11), they did not show a significant fatigue trend except an improvement of the adduction power. The improvement of the adduction power was believed to represent a temporary adaptation trend. In the present

TABLE 5. STATISTICALLY SIGNIFICANT DIFFERENCES BETWEEN MEALS ( $\bar{\Delta}$ ) IN THEIR EFFECT ON VISUAL PERFORMANCE AND FATIGUE TRENDS OF VISUAL FUNCTIONS

FUNCTION	TYPE OF MEAL			
	1 Max. Deter.	2 Min. Deter.	3 $\bar{\Delta}$	4 F
Performance av.....	CHO	Standard	-11.0	8.82*
Performance av.....	CHO	Fat	-8.9	6.45*
Performance range.....	CHO	Standard	-7.5	12.97†
Performance range.....	CHO	Fat	-6.2	(4.89*)
Quest. score.....	no meal	CHO	-5.5	7.64*
f.f.f.....	no meal	Standard	-1.6	8.90*
Brightness discr. green.....	no meal	Standard	-1.6	(4.62*)
Adduct. power.....	CHO	no meal	-5.7	8.68*
Adduct. power.....	CHO	Fat	-3.7	9.92*
Vert. diverg.....	CHO	Fat	-0.3	16.30†
Accom. near pt.....	Standard	no meal	-1.8	7.36*
Accom. near pt.....	Standard	CHO	-1.6	6.99*
Converg. near Pt.....	no meal	Fat	-0.6	(4.08*)

Column 1 shows the meal with the greatest (or greater) degree of deterioration (max.), column 2 that meal with the smaller degree of deterioration (min.), column 3 the difference ( $\bar{\Delta}$ ) between both and column 4 the statistical significance, expressed by the F-test.  $F^* = 4.96$  for the 5 per cent level;  $F^\dagger = 10.04$  for the 1 per cent level; F values near 5% significance are indicated by parentheses.

series, the improvement is present (though statistically not significant) in all types of meals except the CHO meal. The convergence near point shows a highly significant deterioration after no meal and after the CHO meal, while there is no significant change after the standard meal. The experiments in our former study (11) were performed after the standard meal.

Visual fatigue is one of the most important types of fatigue in all jobs requiring the discrimination of fine details (group A and B in the illumination code of the I.E.S., 13). The muscular effort and, consequently, the energy expenditure is comparatively small in this category of industrial occupations, and conceivably the results might have been different in a heavier type of work. However, the energy expenditure is small in the majority of industrial jobs and the present work task is comparable in that respect. Therefore, it seems that our results would have a rather general significance and application in industry. The discrepancy to Haggard and Greenberg's

study on sewing of tennis shoe tops, which also falls in the category of light muscular work, cannot be explained

The results show that the intake of meals is an important factor for visual performance and the fatigue trends of visual functions. The degree of deterioration or, in certain functions, even the direction of changes, depend to a large extent on the type of meal given. So far, little attention has been paid to the effect of environmental factors (external and internal) on visual functions. With only few exceptions, vision has been studied as a function independent of the physiological complex of which it is a part. The limitation of such an approach is apparent. Obviously, the intake of meals must be considered in the standardization of experimental conditions for the study of visual fatigue.

#### SUMMARY

In a type of strenuous visual work requiring the recognition of fine details moving on a conveyor belt, four types of meals (no meal, balanced standard meal, high fat, high carbohydrate) were compared in 6 subjects. In addition to performance criteria and a discomfort questionnaire score, fatigue trends in the blinking rate, several retina functions and several ophthalmological routine tests were studied. Statistically significant differences between various types of meals were obtained in the majority of items, but no type of meal (including no meal) was superior or inferior for all visual functions involved. In general it seems that the standard meal or the high fat meal are preferable for strenuous visual work. The intake of meals is an important factor for the magnitude and direction of changes in visual functions during hard visual work.

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## *Heart Rate in Recovery from Severe Exercise*

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RECOVERY FROM MUSCULAR EXERCISE can be regarded as complete only when every function has returned to its pre-exercise level. In practice, the recovery period has often been regarded as over when oxygen consumption and respiration had returned to normal. After exhausting exercise, however, some factors of the circulation, for instance the pulse rate, do not recover at the same rate as does respiration,  $O_2$  intake and cardiac output (1-3).

It was thought that peripheral vasodilatation might be one factor causing the tachycardia to persist after the other functions had returned to normal. From experiments by Grill (4), it appears that vasodilatation occurs in the muscles of the arm after the exercise has been finished. Mateeff and Petroff (5) and Mateeff (6) have shown that vasodilatation under certain conditions is so pronounced that 'faints' could be produced in subjects left standing after severe exercise. These 'faints' could be prevented by bandaging the legs. Allen and co-workers (7) have confirmed their findings.

An attempt has been made, therefore, to determine to what extent vasodilatation occurred after short exhausting exercise, and whether the duration of the tachycardia could be influenced by preventing the supposed vasodilatation in the legs by bandaging.

### METHOD

Four boys between the ages of 16 and 18, who were well trained in cycling, were used as subjects. Their pulse rate was taken after a 10-minute rest in a horizontal position. The subject was then seated on a bicycle ergometer and started pedalling at the rate of 60 cycles/min. for 5 minutes. The ergometer did not permit the exact determination of the work done. The brakes were therefore set in such a way as to make the work so hard that severe dyspnoea set in during the third minute and continued to the end of the 5-minute period. At this time the subject was near exhaustion. This crude form of standardization had the advantage that the different condition of the subject on different days did not interfere with the outcome. Naturally the state of training varies, and work of such severity will be

tolerated better on one day than on another. Thus it may happen that the same amount of work is done with comparative ease on one day and causes exhaustion on another. It soon became clear that our subjects needed on different days different intensities of work in order to produce the same state of exhaustion within 5 minutes. In order to obtain the same degree of exhaustion, the load had to be varied slightly during the fourth and fifth minutes in some experiments. To measure approximately the magnitude of the work, the  $O_2$  intake was determined in a few instances during the last minutes of work. It lay between 3500 and 3800 cc/min. This requirement would be according to experiments of Christensen (8), equivalent to about 1650 kg.m/min. in subjects not exhausted. In or near exhaustion this oxygen requirement is, according to my own experience, equivalent to a smaller amount of work lying probably between 1200 and 1400 kg.m/min. The basic value of oxygen consumption (not fasting, sitting on the bicycle) was reached in two experiments 43 and 57 minutes after the end of the work.

When the work was finished, the subject lay down and, in about half the experiments, the legs and arms were bandaged from ankle and wrists to groin and axilla, respectively. Three-inch rubber bandages were used and put on so firmly that the feet and hands were slightly congested. In some experiments "pricking" sensations were experienced, but never so strongly that it was necessary to remove the bandages. The pulse was taken with a stop watch for periods of first 10, later of 20 to 30 seconds, at intervals of 2 to 8 minutes. When the basal rate after the exercise was reached the bandages were taken off and the heart rate followed for another 10 to 15 minutes. In most cases the basal rate after the exercise was the same as before. In some it was lower than before, especially when the exercise had taken place an hour after a meal. The value before exercise was, in these cases, probably influenced by the digestive processes. In all cases the level reached after exercise was taken as the resting level. In two subjects the blood pressure was taken in one experiment with bandages and in one without. No significant difference was found.

It seemed of interest to investigate also the volume of the legs before and after exercise. For this purpose a simple leg plethysmograph was constructed from an oil drum which had a height of 96 cm. and a diameter of 25 cm. The top was taken off and an overflow pipe inserted 2 cm. below the rim. The drum was filled with water of room temperature and the subject asked to stand in it. In order that the feet should always be in the same position a large firebrick was placed in the bottom of the drum, which, at its sides, left just enough space for one foot. Before the subject took up his position in the drum, he had to lie down quietly for 10 minutes in order to disperse any blood that might have accumulated previously in his legs by

standing. When the subject had climbed in, more water was quickly run in until it began to drip slowly from the overflow. This process took 1 to 2 minutes; the subject was then asked to lie down again for 6 to 7 minutes. Then he climbed in a second time, and the water level was again adjusted until the overflow began to drip. The subject now remained standing in the drum for exactly 10 minutes. The water was dripping continuously during that time and its amount was measured and put back. Immediately afterwards the subject did 5 minutes of exhaustive exercise, either on the bicycle or by stepping up and down a stool and a shelf of 1-meter height. Then he re-

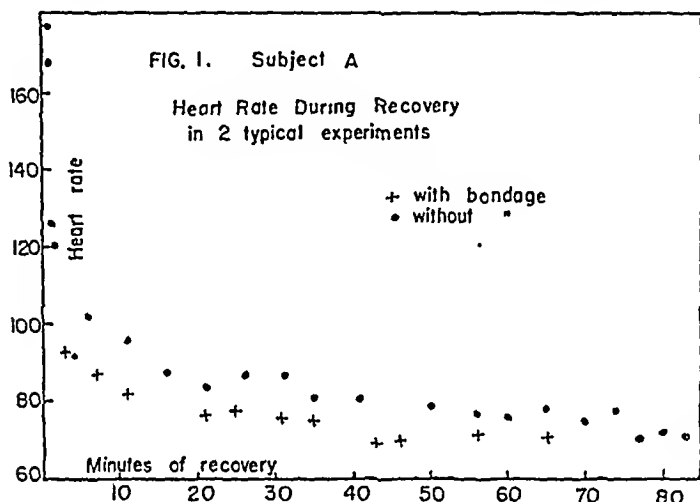


Fig. 1

sumed his place in the drum for another 10 minutes and the displaced water was again measured. The water temperature was between 70° and 75°F., and the change from the beginning to the end of the 10-minute period was never more than 0.5°F., taken near the subject's legs. Stirring the water was not possible as it would have influenced the overflow.

### RESULTS

The results of the experiments with heart rate recovery are shown in figures 1 and 2. Figure 1 shows two typical experiments of the *subject A*. Figure 2 shows the times at which all 4 subjects reached their resting values with and without bandages. There is a significant difference; the recovery with bandages took less time than without. In only two cases did the recovery time with bandages lay comparatively close to the controls. These two experiments were made shortly after the Christmas holidays and it is possible that, because of the lack of training, the work was comparatively harder than in the controls, which had been done some time before. At least the



subjects stated after the work was finished that they felt more exhausted than in the former experiments, during which they had been in better training.

The plethysmographic experiments show a very uniform result. There was an increase in the volume during standing after rest, which was due mainly to the hydrostatic pressure of the blood and was to be expected according to the experiments of Atzler and Herbst (9). After exercise the increase was, in all cases, much greater; although the variations were rather large, there was always an increase, on the average 275 cc. A correction for the increase in temperature is not necessary, as the increase was practically

TABLE 1. PLETHYSMOGRAPHIC EXPERIMENTS

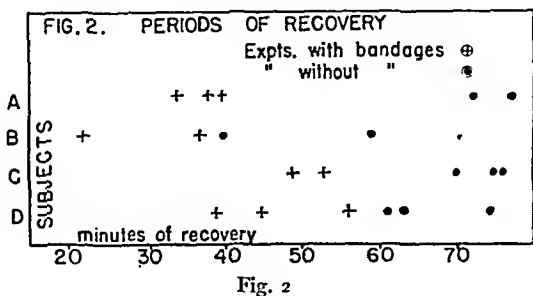
SUBJECT	WATER DISPLACED IN 10 MIN. AFTER REST	WATER DISPLACED IN 10 MIN. AFTER EXERCISE	DIFFERENCE cc.
	cc.	cc.	
<i>Ca.</i>	230	520	290
	470	640	170
<i>H.</i>	320	550	230
<i>By.</i>	160	310	150
	210	350	140
<i>Gi.</i>	212	590	378
	240	580	340
<i>Ga.</i>	155	830	675
<i>T.</i>	130	435	305
<i>Cr.</i>	230	305	75

the same in both 10-minute periods. A further correction for the amount of water taken out of the drum by the subject, when stepping out in order to do the work, should be made. This amount was estimated by drying the subject's legs with a towel and weighing the towel before and afterwards. The amount of water thus lost was found in two experiments to be 32 and 38 grams. A similar amount (35 cc.) should, therefore, be added to the increase in leg volume after exercise. Subject *Ga* had an especially large increase, 675 cc. This subject, a medical student, stated that he had always been conscious of very heavy and even slightly swollen legs after competitive running events.

#### DISCUSSION

It can be regarded as certain that substantial amounts of blood may be retained in the muscles of the extremities by vasodilatation (10, 11). It is also certain that such a vasodilatation occurs in recovery from severe exer-

cise (5, 6). The amount of blood pooled under such conditions probably varies greatly, as the latter authors could produce 'faints' only in about 20 per cent of their subjects. It varied greatly also in the experiments of Ebert and Stead (12), who pooled blood in both legs and one arm by venous congestion and found an average of 720 cc. In 4 of their 7 cases circulatory shock occurred. Great variation is seen also in our experiments. The average of 300 cc. for both legs is smaller than in the experiments of Ebert and Stead, probably because in venous congestion the blood is pooled not only in the muscles but also in the other tissues of the limbs. The 300 cc. pooled in the legs may not represent the whole amount withdrawn; if the



increased amount of lactate in the blood after exercise is responsible for the vasodilatation, as it may well be according to the experiments of Domini and Rein (13), a dilatation in the other skeletal muscles is likely. If a total of 400 to 500 cc. of blood is withdrawn from the general circulation, it will necessarily influence its mechanics, although it may not have the drastic results of larger amounts.

There can be no doubt that in our plethysmographic experiments a vasodilatation occurred which was large enough to influence the general circulation. These experiments do not permit, however, to say how long this vasodilatation lasts. The method of bandaging the limbs which we have used to answer this question is comparatively crude. Neither standardization of the work nor of the pressure of the bandages has been possible. Whether the former can be achieved with maximum exercise, where state of training and general condition of the subject vary so greatly, is doubtful. But maximum exercise must be used, or otherwise the periods of recovery will not be long enough to show significant differences. The differences found in our experiments with bandages are great and fairly regular, and they show that compression of the peripheral vascular bed abolishes the excessive duration of the tachycardia. This in itself is not direct evidence for the persistence of peripheral vasodilatation, and does, therefore, not prove that this is the cause of the tachycardia.

There is, however, some other indirect evidence. After severe exercise the heart shadow decreases in size (14). This has been confirmed by many observers and it has also been found in cinematographic investigations (15)<sup>1</sup>. A probable reason for this is a diminished venous return caused by peripheral vasodilatation. The heart adapts itself to a decreasing amount of blood by a decrease in size (16), and the stroke volume falls. In order to maintain a sufficient cardiac output the heart rate has to remain increased as long as the peripheral pooling of blood lasts.

The final proof for the assumption that vasodilatation is indeed the cause of the persistent tachycardia would be the production of the tachycardia by experimental vasodilatation in the limbs. This proof, however, is difficult, as Eichna, Horvath and Bean (17) have produced tachycardia by venous congestion only when standing was added to the congestion. It is possible that the circulatory regulation acts differently in the active vasodilatation and the passive venous congestion.

#### SUMMARY

In four subjects the pulse rate returned more quickly to normal after severe exercise when the extremities were compressed by bandaging. Experiments with a simple leg plethysmograph showed that the leg volume increased after severe exercise.

The relation of these observations to the persistence of a frequent heart rate after severe exercise is discussed.

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<sup>1</sup> This decrease in heart size may last for hours after the end of exhausting exercise.

# *Experiments with the Eve Method of Artificial Resuscitation*<sup>1</sup>

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THE ROCKING METHOD of artificial resuscitation which was introduced by Eve (1) has been the subject of much interest and investigation. Killick and Eve (2) evaluated the efficiency of the method in terms of the volume of air moved per minute, the amount of oxygen absorbed and the carbon dioxide content of the expired air. They reported that the method was as effective as the Schäfer procedure in terms of tidal air movement. Waters and Bennett (3) observed a single subject and did not find the procedure in terms of tidal air movement as satisfactory as the Silvester or Schäfer methods. Macintosh and Mushin (4) studied the procedure under supposedly ideal conditions and found that in terms of tidal air it was about as good as the Schäfer and Silvester methods.

Many suggestions regarding the apparatus to be used have been repeatedly made; the essential equipment remains, however, a see-saw rocker device which is easily constructed by placing a stretcher on a wooden horse. Eve (5) explains clearly the circulatory effects he attributes to his method in another paper. Hemingway and Neil (6) in experiments upon dogs concluded "that the rate of oxygen uptake and the cardiac output are usually greater with the rocking method than with the Schäfer." Eve (5) reported that in 1943 the method was adopted by the Royal Navy as the preferential method of artificial resuscitation, the Schäfer procedure being employed until the Eve apparatus is set up—usually a matter of seconds.

It seemed of value to study the efficiency of the method from certain aspects and with certain variations in technique. To this end we have carried out a group of experiments designed to test further the efficiency of the

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<sup>1</sup> A preliminary report of some of this work was presented in *Federation Proc.* 6 (1), March 1947.

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<sup>5</sup> The experimental work was conducted in the Physical Fitness Laboratory at the Long Island College of Medicine, Brooklyn, N. Y.

method, which presently appears to be the best technique of simple manual artificial resuscitation.

Five different types of experiment were performed: 1) experiments to compare the machine tidal air and minute volume with normal resting values in different subjects; 2) experiments to compare the alveolar  $\text{CO}_2$  and  $\text{O}_2$  existing after a period of rocking with the resting prerocking values; 3) experiments to study the effect of altering the rate and acceleration of rocking on tidal and alveolar air values; 4) experiments on subjects during apnea<sup>6</sup> to test further the efficiency of the rocker in producing an adequate movement of air into and out of the lungs; 5) experiments to study the effect of rocking on cardiac output.

#### GENERAL PROCEDURE APPARATUS

The apparatus consisted essentially of a see-saw rocker mounted upon a support as shown in figure 1, so that it could be rocked back and forth to an angle of  $50^\circ$  from the horizontal. At the head end of the rocker a suitable framework was clamped in position to provide support for the manifold shown in figure 2. This consisted of a straight brass tube with a one half-to three fourths-inch inside diameter, equipped at both ends with rubber flutter valves (*B*) and (*G*) to prevent backward movement of air. The subject was attached to the outlet (*D*) by means of the rubber mouthpiece (*E*). Thus, when a nose clip was placed on the subject, inspired air entered through *A* and expired air passed through *H*, which was attached to a spirometer for recording the tidal air and minute volume. The valve at *C* was a shut-off valve which could be closed whenever an alveolar air sample was taken through the outlet *F*. A 100-lb. weight placed at the foot end of the device counterbalanced the weight of the respiratory apparatus at the end near the operator and made for ease of operation.

The subjects, students at the Long Island College of Medicine, were random selections in normal health, and no subject was used more than once for the work reported, in any phase whatever.

The subject was placed in a supine position upon the rocker with the feet firmly braced against the foot board. The tie and belt were loosened and the hands and feet strapped to the stretcher frame to prevent sliding during the rocking (fig. 1). Before each experiment was begun, the subject was allowed to breathe through the entire apparatus for a few minutes with the nose clip on, in order to become adjusted to the conditions. Every possible effort was made to make him comfortable and free from apprehension. He was instructed to forget about his respiration, to relax, and to let the machine do the work during the rocking period.

<sup>6</sup> This was actually in most subjects just a marked depression of respiration, *relative apnea*. However, in a limited number of subjects it was possible to obtain total cessation of respiration, *apnea vera*.

Tidal air and minute volume measurements were made by collecting the expired air in a calibrated recording spirometer. Alveolar air samples were analyzed in an ordinary Haldane type of apparatus immediately upon withdrawal of samples (fig. 1).  $\text{Ca(OH)}_2$  was used for  $\text{CO}_2$  absorption and Oxsorbent,<sup>7</sup> a commercial reducing agent consisting of a stabilized solution of chromous chloride, for the  $\text{O}_2$ . All gas values have been corrected to standard temperature and pressure.

Except where noted, all rocking was done at a rate of 12 cycles per minute according to a stop watch and with a minimum acceleration. A cycle consists of two phases of rocking, one with the head depressed and the other with the head elevated. The values obtaining from any rocking procedure will be termed *machine rocking values* and the values without rocking, *resting values*. The maximum angle of tip from the horizontal was 30 degrees in all cases.

Several variations from the original suggestions of Eve have been used herein and should be mentioned. He suggested regular rocking at a rate between 10 and 15 times per minute at an angle between 45 and 90 degrees with the subject in the prone position. Our subjects rested on the stretcher in the supine position, in order to facilitate the recording of tidal air and minute volume and the obtaining of alveolar air samples. In as much as occasion for continued use of the procedure may arise in an emergency, the angle of tip which did not tire the operator by forcing him to bend excessively was chosen. It was 30 degrees either side of the horizontal. Further comment upon the effect of position of the subject and the angle of tip is offered in a later section.

#### RESULTS AND DISCUSSION

In all methods of artificial respiration, Hemingway and Neil (6) find two considerations paramount. *a*) Sufficient pulmonary ventilation must be brought about by the resuscitation method in use to reactivate the respiratory center, which will eventually assume its normal function and in turn bring about normal respiration. *b*) A method must be present for the restoration of the transport of blood gases to the lungs from the tissues. In addition an adequate circulatory system plays a special rôle in bringing oxygen to the respiratory medullary center and keeping it viable. That rapid irreversible damage to the medullary respiratory center occurs is shown by the fact that Ross (7), in reviewing the literature on artificial resuscitation, found that "no instance of revival was reported in which more than 15 minutes elapsed between the cessation of breathing and the start of artificial respiration."

<sup>7</sup> Personal communication with the Burrell Technical Supply Co., Pittsburgh, Pa., manufacturers of Oxsorbent.

### *Experiment One*

When the subject had been accustomed to the rocker and mouthpiece, a recording of his normal tidal air or minute volume was made. The time at which this was done was not told to the subject. After three and again after four minutes rocking, a 30-second record was made of the rocking tidal air or minute volume. In one group of 17 subjects the effect of rocking on tidal air was measured and in another group of 21 persons the effect on minute volume was observed.

The increase in tidal air movements and the change in minute volume due to rocking are shown in table I. It is interesting to note that the amount of air moved in a minute due to normal respiratory activity was

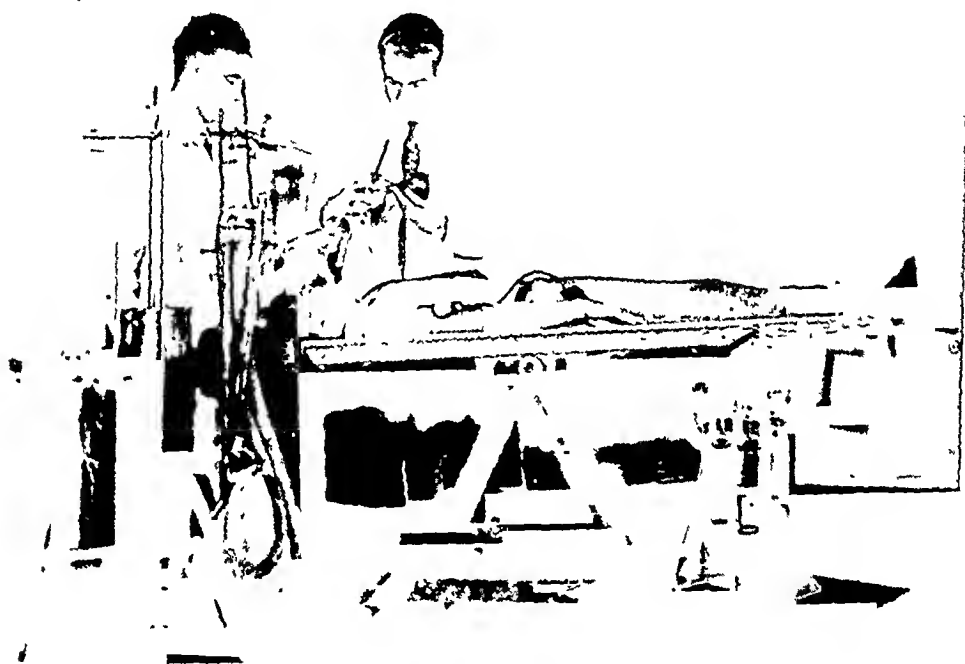


Fig. 1. APPARATUS USED. For discussion, see text.

closely approximated by the machine in many cases with its higher tidal air values and fewer respiratory cycles. In all cases there was an increase in the tidal air due to the machine, except in one subject where the normal and rocking values were identical, and in all cases but one there was an increase in minute volume with rocking.

The tidal air is not indicative of the amount of fresh gas reaching the lung alveoli for gaseous interchange with the blood, for about one fourth of this rests in the dead spaces of the respiratory tract. There is normally about 350 cc. available for alveolar blood respiratory exchange. The normal tidal air value is about 500 cc. Our subjects averaged about 1200 cc. machine tidal air. The increase of 700 cc. in tidal air represents a 140

per cent increase due to the machine. Yet, the increase of the dead space due to the machine is merely the volume of the gas resting in the manifold arms, *D* and *G*, which amounts to about 50 cc. It thus becomes more accurate to calculate the air available for use when the machine is used by deducting the sum of the normal and machine dead space, 200 cc. from the total tidal air due to the machine's use, 1200 cc. If the 1000 cc. resulting now be compared to the amount of air normally available for respiration, 350 cc., it is apparent that the real increase in tidal air due to the machine is 185 per cent. In the more than normally distended alveoli the area for blood gas exchange is also increased.

### *Experiment Two*

Little value would accrue from the enhanced tidal air values caused by the machine respiration if it also caused an aphysiological change in the alveolar gas levels. The return to normal respiration as a result of medullary control is influenced by the pH of the blood in the medullary tissue and carotid sinus. If, after the initial washing out of the accumulated CO<sub>2</sub> caused by previous respiratory cessation the machine were to depress the CO<sub>2</sub> level much below the normal, the pH of the blood would not exert the stimulus on the carotid body and medullary respiratory center necessary for the return of normal respiration. In addition, it must be pointed out that a significant reduction in alveolar CO<sub>2</sub> and the subsequent development of acapnia of prolonged extent may be fatal. Contrasted to the widely accepted theory of dual control of respiration just mentioned is the recent work of Heymans (8) who has shown that within physiological limits the effect of blood pressure and CO<sub>2</sub> is negligible centrally, whereas the real control is exerted by the actions of these factors on the carotid and aortic bodies. In both explanations, however, the importance of the CO<sub>2</sub> level is stressed. Analysis of the alveolar gas levels was made to further study the effect of rocking on the subject, and the contrast between the subject's usual values and that obtained during rocking provides a guide to evaluating the efficiency of the machine in stimulating the normal respiratory mechanism.

Lying flat on his back, the subject exhaled completely and nodded at the termination, at which time a sample of the residual alveolar air was obtained by means of a rubber suction bulb. Subsequently the subject was rocked as described above, and after three minutes was brought to a horizontal standstill for a few seconds in order to draw the alveolar sample. The bulb was placed in proper position during the rocking in order to minimize the possibility of the subject's voluntarily breathing before the sample was taken.



The effect of rocking upon the alveolar air as compared with resting values in 17 subjects revealed a mean resting alveolar volume percentage of 14.19 and 5.20 and rocking values of 14.09 and 5.20. The regular rate of rocking did not alter alveolar gas levels considerably.

TABLE 1. EFFECT BY ROCKING UPON TIDAL AIR AND MINUTE VOLUME IN TWO GROUPS OF DIFFERENT SUBJECTS

NO.	TIDAL AIR IN CC.			MINUTE VOLUME IN CC.		
	Resting	Rocking	% increase	Resting	Rocking	% increase
1	708	3280	311	7000	7400	6
2	430	1430	233	6400	8800	38
3	462	1028	122	7000	8200	17
4	320	746	133	7700	9500	23
5	396	1674	323 <sup>1</sup>	6200	10800	174 <sup>1</sup>
6	461	1700	271	5400	6500	20
7	731	1264	73	5400	6600	22
8	402	1250	155	7500	8500	13
9	580	1421	141	7000	10000	43
10	613	1595	160	6800	9600	41
11	622	1280	106	6800	7700	13
12	620	1631	159	6900	8200	20
13	801	1681	110	6600	9000	36
14	340	828	137	9000	8700	-4
15	480	480	0	10100	11090	10
16	851	865	2	8690	10300	19
17	420	730	74	8225	9150	11
18			137.0±59.2 $\sigma = 273^{\circ}$	7360	8490	14
19				6300	7230	15
20				5200	6170	19
21				6150	7600	23
						25.5±11.1 $\sigma = 11.1^{\circ}$

<sup>1</sup> Excluded from calculations by Chauvenet's criterion.

### Experiment Three

The rocking angle of the apparatus, the position of the subject, rate of rocking and acceleration may be changed independently, or in combination. Waters and Bennett (3) showed that in the one case they studied, the change of the tip angle from 60 to 90 degrees increased the tidal air from 100 cc. to 150 cc. with the patient in the prone position. Macintosh and Mushin (4) noted an increase in the tidal air of one patient from 340 cc. to 580 cc., and in another from 725 cc. to 850 cc., with the subject in the prone position and the angle of tip changed from 60 to 90 degrees. The same patients showed, when the same angle of change was used and they were in the supine

position, an increase in tidal air from 240 cc. to 380 cc., and from 570 cc. to 635 cc. It appears that the angle of tip and the position, as expected, do markedly effect the lung ventilation achieved in the Eve procedure. It is further of significance that the prone position is more desirable in addition to the ventilation increase noted above, in that materials tending to occlude or obstruct the air way, as drowning fluids or gastric contents, are best drained in this position. In addition, the chance of occlusion of the air way due to a flaccid glottis is reduced.

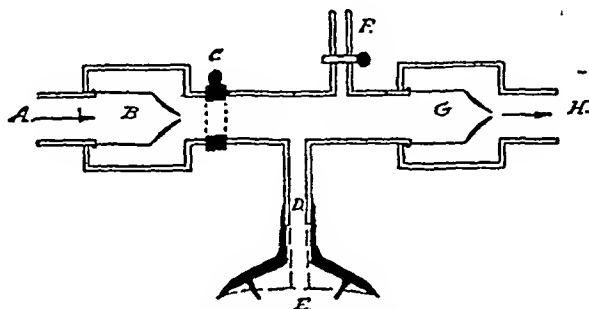


Fig. 2. GAS SAMPLING MANIFOLD. Described in detail in the text.

Relative to the rocking we selected the most extreme possibilities for experimentation since they were most conducive for recording, but there is much need for study of the milder variations. If the subject were rocked so that his acceleration were minimum, the method would correspond to the steady rate of rocking originally suggested by Eve. There is also the possibility of speeding the trip across the horizontal plane and the acute small angles on either side, and permitting the patient to remain for a longer time in the position with the head or feet depressed. This method involves more or less snapping of the subject on the rocker with much variation in acceleration. Killick and Eve (2) observed that as the rate of rocking increased there was an increase in minute volume and also a decrease in the tidal air. They also concluded that the rhythm of rocking had no effect as long as there was sufficient time for the subject to take an adequate inspiration.

A few experiments were made to compare the changes effected in the tidal and alveolar air values when the rocking rate and acceleration were varied. The subject lay in the usual fashion on the rocker and his resting tidal and alveolar air values were recorded. A period of rocking at 12 times per minute with minimum acceleration, termed 'regular rocking', then followed, and after two minutes, the subject's alveolar and tidal air values were again measured. The subject then rested on the horizontal rocker with the nose piece and mouthpiece removed for five minutes. He was then rocked with the mouthpiece and nose clip in place at 12 times per

minute by a procedure of 'snap rocking'. The length of the cycle was the same as with regular rocking, but more time was spent with the head or feet depressed. At the end of two minutes of such rocking, the alveolar and tidal air values were recorded. The subject again rested for five minutes, after which the entire procedure was repeated with the rocking at 6 times per minute instead of 12.

The records of the alveolar and tidal air values obtained when the acceleration and rate of rocking were varied do not seem to indicate any definite benefit was derived from a procedure at 30 degrees maximum angle.

TABLE 2. INFLUENCE ON TIDAL AIR AND ALVEOLAR AIR OF CHANGING THE RATE AND ACCELERATION OF ROCKING WITH THE ANGLE OF TIP 30 DEGREES

NO.	RESTING			ROCKING 12/MIN.			SNAPPING 12/MIN.			ROCKING 6/MIN.			SNAPPING 6/MIN.		
	O <sub>2</sub>	CO <sub>2</sub>	T	O <sub>2</sub>	CO <sub>2</sub>	T	O <sub>2</sub>	CO <sub>2</sub>	T	O <sub>2</sub>	CO <sub>2</sub>	T	O <sub>2</sub>		
1	14.12	5.20	340	13.90	4.80	780	13.80	5.04	1150	14.30	4.95	1181	14.10	4.82	1425
2	14.30	4.87	480	13.80	5.04	480	14.40	4.83	525	13.95	4.75	771	14.02	4.79	650
3	13.70	5.42	621	14.04	5.02	851	13.50	4.91	765	13.90	4.78	525	14.00	4.87	1075
4	14.08	4.38	550	13.64	4.95	755	13.61	4.91	733	13.90	4.79	595	13.70	5.95	483
5	13.79	5.20	513	13.94	5.37	595	13.64	4.87	613	13.94	5.16	641	13.52	5.95	884

T = tidal air, values in cc. The alveolar values are given in volumes per cent.

The tidal and alveolar air values varied without any particular relationship to the method of rocking (table 2). Macintosh and Mushin (4) found however, that with 'jerky' rocking, which they do not define but which probably had variations in acceleration, there was about 15 per cent decrease in tidal air moved as contrasted to smooth rocking. However, it is evident that in any method attempted by us, the alveolar air values were within physiological limits and the tidal ventilation was adequate. Killick and Eve (2) have investigated the effect of various rates of rocking and asserted that "at a rate of above 15 per minute there is a tendency to overventilate and hence wash out carbon dioxide in amounts disproportionate to the amount of oxygen which can be absorbed."

A number of subjects commented upon the feeling of being rocked. Most of them found the regular rocking pleasant and believed that they would fall asleep if it were continued. In two subjects headaches disappeared while being rocked. One subject gradually became dizzy and felt faint when rocked regularly, necessitating termination of the procedure. However, it was subsequently shown that he may have relatively ineffective neurocirculatory balance, for he promptly fainted when motionless on a tilt-table at an angle of 55 degrees.

The subjects found the snap rocking less agreeable than the regular procedure, with particular dislike for the head being snapped into the down

position. Of course, this subjective feeling is not a factor in unconscious persons upon whom the method is used as an emergency procedure. The one subject who exhibited poor neurocirculatory balance tolerated only two snap rocks, and then became so dizzy and weak that the procedure was terminated.

### Experiment Four

The best experimental data would be obtained directly from patients needing artificial resuscitation, but such were not available. It was realized that the volitional element present in the conscious subject might be in-

TABLE 3. TIDAL AIR AND MINUTE VOLUME

	RESTING %	WITHOUT RELATIVE APNEA %	WITH RELATIVE APNEA %		
Means					
Minute.....	100	117.5	116.7		
Tidal.....	100	151.8	152.8		
<i>Alveolar CO<sub>2</sub> in Volumes Per cent</i>					
	RESTING %	(A) AFTER ROCKING %	(B) AFTER HYPERPNEA %	WITHOUT ROCKING %	
Means.....	100	67.25	80.96	69.09	85.24
P.E.....		±.63	±.77	±.60	±.97
		4.49	5.64	4.38	7.02

$$A_{\text{mean}} - B_{\text{mean}} > \pm 3\sqrt{(PE_A)^2 + (PE_B)^2}$$

For explanation of table 3, see text.

fluencing the results. In addition, Henderson (9) has noted that the tonus of the respiratory muscles of a conscious subject varies so much that the respiration minute volume is the same whatever rate or method is used. The use of patients in the deep stages of anesthesia was not possible. We tried to gain the subject's confidence in the machine before experimentation so as to minimize the possible voluntary effect on breathing.

In order to more accurately measure the efficiency of the machine in terms of tidal air, volume of air moved per minute and also the effect on lung gas levels, the following procedure was carried out. The subject was placed on the stretcher in the usual position, with a pneumograph strapped about the chest at the point of greatest respiratory movement and connected with a recording tambour-lever apparatus. The record was made on a slowly revolving kymograph. Resting tidal air and minute volume were also recorded. The subject was then rocked in the regular fashion and rate, and at the end of three minutes his tidal air and minute volume were again recorded. After a period of five minutes rest, the subject entered into a 3-minute period of hyperpnea and at the end of this period

simply relaxed. He was found to be, in most cases, in a state of relative apnea, as indicated by minimal movement of the recording lever on the kymograph and observations of the chest movements. A sample of post-hyperpneal alveolar air was immediately obtained. The subject was then regularly rocked at 12 times per minute while the tidal and minute volume were recorded, thus giving these values during a period of relative apnea. At the end of one minute of rocking a second sample of alveolar air was taken.

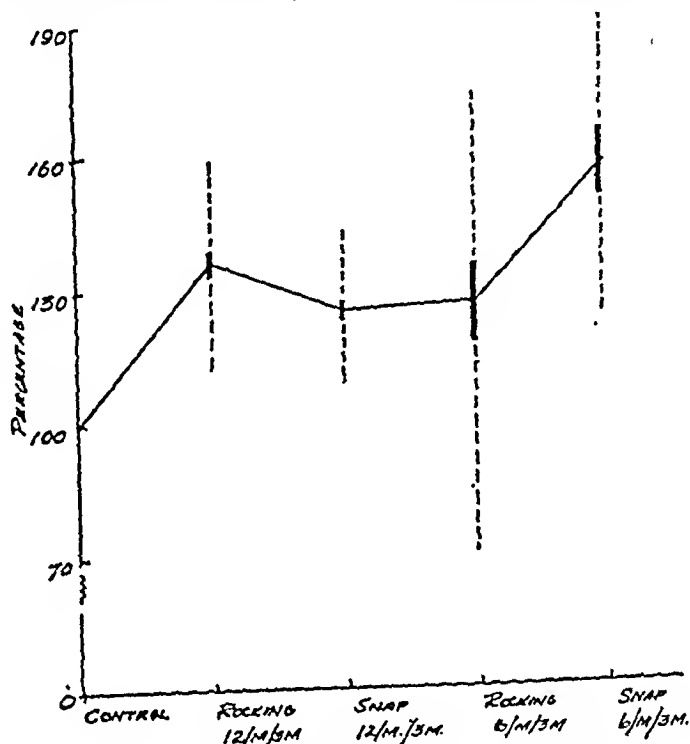


Fig. 3. INFLUENCE OF ROCKING upon cardiac output.

After a ten-minute rest period, the subject was again put into a three-minute period of hyperpnea, and the procedure repeated except for the rocking which was omitted.

In another group of experiments, the record of hyperpnea and apnea was observed by means of a recording spirometer. In a few subjects, it was possible to obtain true apnea.

The procedure in which relative apnea was used is a modification of the work of Waters and Bennett (3) who hyperventilated artificially patients under moderately deep anesthesia. In such apneic patients, whom they believe exactly simulate candidates for artificial resuscitation, they found the Silvester procedure best from the point of view of tidal air, and the Eve procedure to produce a tidal air of about 100 to 150 cc.

More ideal conditions were created by Macintosh and Mushin (4) who deeply anesthetized subjects so that breathing stopped and artificial respiration was essential for the preservation of life. They observed that

the Schäfer, Silvester and Eve procedures produced about the same result in terms of tidal air movement and concluded that the "choice of any particular method appears to be relatively unimportant. If the subject is dead no method will be availing, and speaking broadly, if a spark of life still exists, any method properly carried out will probably suffice." It is difficult to explain the disparity of tidal air values between 100 cc. to 150 cc. in Waters and Bennett's work and 240 cc. to 850 cc. in Macintosh and Mushin's work, solely on the degree of anesthesia of the subjects.

TABLE 4. EFFECT OF ROCKING, BOTH SNAP AND REGULAR, ON CARDIAC OUTPUT, AS INDICATED BY THE CARDIAC INDEX

RESTING 100%	REGULAR ROCKING	SNAP ROCKING
	%	%
6/min. for 3 min.	Mean = 127.6 P.E. = $\pm 10.0$ $\sigma$ = 57.3	Mean = 158.8 P.E. = $\pm 6.4$ (A) $\sigma$ = 34.2
12/min. for 3 min.	Mean = 136.1 P.E. = $\pm 3.8$ $\sigma$ = 23.3	Mean = 125.5 P.E. = $\pm 2.5$ (B) $\sigma$ = 15.1

For further explanation see text. It will be seen that applying the criterion of significance snap rocking at 6 per minute for 3 minutes was significantly effective.

$$A_{\text{mean}} - B_{\text{mean}} > 3 \sqrt{(PE_A)^2 + (PE_B)^2};$$

in fact, it is 4.8 times greater.

The values of tidal air with and without apnea showed a similarity in the increase due to rocking. The minute volumes were somewhat more than the resting (table 3). Since the relative apnea reduced the possibility of any voluntary effect upon breathing, and since the values obtained with and without relative apnea were very similar, the validity of the results in the first experiment is enhanced.

Further indication that the rocking procedure does not depress the alveolar  $\text{CO}_2$  level appreciably is shown by the steady rise in this factor from the low post-hyperpneal level as the rocking procedure continued. Comparison of this rise with that when the subject was not rocked following hyperpnea shows that there is some delay caused by the rocking, as might be expected from the greater lung ventilation.

### *Experiment Five*

In order to study cardiac output in a qualitative sense the method of Erlanger and Hooker (10) was used, by which the status of the cardiac output is suggested by the changes in the cardiac index, which is itself the

product of pulse pressure and heart rate. Skelton (11) showed that if peripheral resistance remains constant, the procedure gives a rough guide to the activity of the heart, for the index and output always change in the same direction. In our experimental work the only variable was the rocking. The effect of nervous anxiety on peripheral resistance was in the main eliminated by allowing sufficient time for the subject to adjust to the conditions of the experiment.

The subject lay on the stretcher in the usual fashion and rested for 10 minutes until a rather constant control blood pressure was obtained. In addition, resting tidal, alveolar air and minute volumes were obtained. Regular rocking was done for three minutes at 12 times per minute rate, with sporadic samples of tidal air and minute volume being recorded. At the end of three minutes rocking alveolar  $\text{CO}_2$ ,  $\text{O}_2$ , blood pressure and pulse were obtained. The subject then rested for ten minutes without mask and nosepiece. The procedure was then repeated for 12 per minute snap, 6 per minute regular and snap rocking, with a rest of ten minutes between each procedure.

The results indicate an increase in cardiac output, the prime factor associated with this probably being the increased venous return due mostly to the effect of gravity and the momentum of rocking in returning the blood to the heart (5).

Hemingway and Neil studied the rocking procedure in dogs. When deeply nembutalized the dogs showed a decrease in respiration and cardiac output to about one half of normal. With pump artificial respiration, the respiratory action could be brought to about normal, but negligible effect on cardiac output occurred. With rocking the cardiac output was returned almost to normal. By the Bainbridge reflex, the increased venous inflow to the great veins of the heart causes increased heart rate and thus increased cardiac output in most cases. One would expect that the deep inspiration noted in the rocking procedure would be accompanied by decreased intra-thoracic pressures, thus enhancing venous return.

Figure 3 and table 4 show the effect of rocking on cardiac output. In general with our normal subjects, the cardiac output was increased by rocking. Thus one may infer that there would be this same augmentation of the subnormal cardiac output in the patient needing resuscitation.

The operator found the method easy, and the 12 per minute regular rate could be approximated accurately by chanting the Red Cross standby "in goes the good air; out goes the bad air," to each cycle of the machine.

## SUMMARY

Evidence is offered to show that the Eve method of artificial resuscitation provides adequate ventilation of the lungs. The rocking tidal air values were greater than the resting values for the subject. Alveolar gas analyses indicated that aphysiological gas levels were not created in the lungs. The Eve method does not cause discomfort to the patient.

The possibility for varying the rate and/or the acceleration of rocking has been suggested. Preliminary experimental results along this line are variable but seem to indicate that the 12 per minute regular rate of rocking with minimal acceleration and with a maximum angle of 30 degrees tip is satisfactory. The adequacy of the rocking procedure was evaluated in some subjects in states of true and relative apnea. The increases in tidal air and minute volume were about the same as obtained without relative apnea. With rocking the return to normal of the post-hyperpneal alveolar  $\text{CO}_2$  was somewhat slower than without rocking, reflecting a greater ventilation of the lungs. The rocking procedure enhances cardiac output, and thus aids in the restoration towards normal of the lowered cardiac output found in persons needing artificial resuscitation.

The authors wish to thank the late Dr. G. B. Ray and Dr. J. R. Johnson, former members of the Physiology Department of the Long Island College of Medicine, for their suggestions and for laboratory facilities for this work. Dr. Johnson is now Professor of Physiology at the University of Ottawa, Canada. The senior author wishes to thank Dr. R. S. Aaron, who stimulated his interest in the Eve procedure, and also made available some of the apparatus used in this study. The authors also express gratitude to the Brooklyn Edison Gas Co. for constructing the rocking device.

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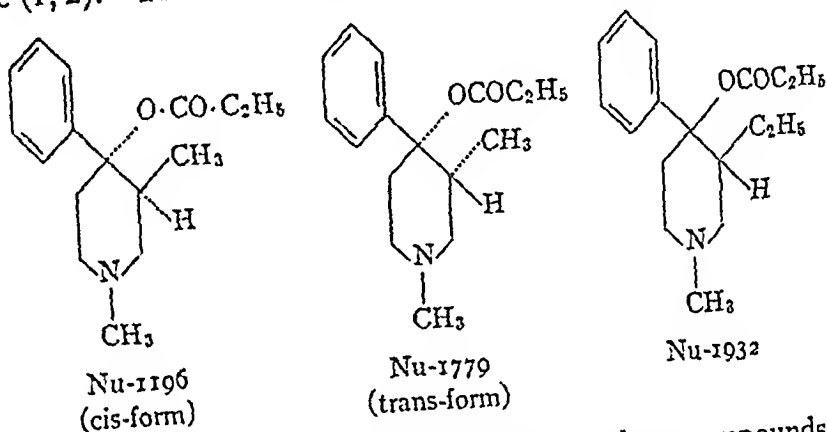
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## Human Studies on Analgesic Piperidine Derivatives<sup>1</sup>

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**D**URING THE LAST YEAR we have had occasion to study three new analgesic compounds of the piperidine type, namely, *a*) Nu-1196, dl- $\alpha$ -1,3-dimethyl-4-phenyl-4-propionyloxy-piperidine hydrochloride, *b*) Nu-1779, dl- $\beta$ -1,3-dimethyl-4-phenyl-4-propionyloxy-piperidine hydrochloride, and *c*) Nu-1932 dl- $\beta$ -1-methyl-3-ethyl-4-phenyl-4-propionyloxy-piperidine hydrochloride (1, 2). The formulae for these compounds are as follows:



Randall and Lehmann (2) have made studies on these compounds relative to analgesia in the rat. They report that Nu-1196 has about the same analgesic potency as morphine, Nu-1779 and Nu-1932 are about five times as active as morphine in rats.

With the apparent high potency and analgesic activity of these compounds it became of interest to study their activity in normal human subjects, since the primary use of analgesics is to control pain in the human being. These studies were undertaken with the view that they may furnish some guidance as to the suitability and relative activity of these agents. The final confirmation of efficiency and other requisites must be determined in the clinic.

The method used was that of Hardy-Wolff-Goodell (3) and consisted of serial determinations at 20-minute intervals of the percentage rise in pain threshold over a suitable period.

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The above three agents were compared with morphine with respect to the peak threshold rise, time to reach peak threshold rise and duration as determined by the time to fall to 10 per cent of the peak threshold rise. Each subject maintained a record of his subjective symptoms, with minimal suggestions or questioning on the part of the operator. Independently the objective signs were noted at suitable intervals by the operator.

Medical students were found to be particularly reliable in these studies because of their great interest in the drug effects. All students were trained

TABLE 1. COMPARISON OF ANALGETIC POTENCIES UPON SUBCUTANEOUS INJECTION

S.C. DRUG	DOSE	N	HEIGHT PEAK % RISE THRESHOLD $M \pm \sigma^1$	TIME TO REACH PEAK $M \pm \sigma^1$	DURATION TO 10% OF PEAK $M \pm \sigma^1$
	mg.			min.	min.
Morphine SO <sub>4</sub>	5	5	13.8 $\pm$ 2.1	64.0 $\pm$ 8.0	185 $\pm$ 14.2
Morphine SO <sub>4</sub>	10	6	21.5 $\pm$ 1.9	73.3 $\pm$ 9.8	246 $\pm$ 33.2
Morphine SO <sub>4</sub>	15	5	27.2 $\pm$ 2.5	84.0 $\pm$ 7.7	280 $\pm$ 7.4
Nu-1779	5	7	9.5 $\pm$ 1.6	63.0 $\pm$ 12.3	144.0 $\pm$ 23.7
Nu-1779	10	7	17.8 $\pm$ 2.7	65.8 $\pm$ 8.9	204 $\pm$ 28.2
Nu-1779	15	9	25.6 $\pm$ 4.3	53.4 $\pm$ 8.8	285 $\pm$ 27.8
Nu-1196	5	6	7.6 $\pm$ 1.2	53.4 $\pm$ 9.4	119 $\pm$ 11.7
Nu-1196	10	8	17.2 $\pm$ 1.8	57.5 $\pm$ 6.6	191 $\pm$ 20.5
Nu-1196	15	7	21.4 $\pm$ 2.0	54.2 $\pm$ 14.6	235 $\pm$ 34.6
Nu-1932	1.0	9	13.1 $\pm$ 4.6	26.7 $\pm$ 6.4	107 $\pm$ 9.7
Nu-1932	2.5	9	18.0 $\pm$ 6.4	22.3 $\pm$ 6.2	137 $\pm$ 7.5
Nu-1932	5	8	19.8 $\pm$ 1.0	55.9 $\pm$ 28.4	197 $\pm$ 46.9
Nu-1932	10	8	18.6 $\pm$ 4.5	57.6 $\pm$ 29.0	225 $\pm$ 13.3
Nu-1932	15	13	22.8 $\pm$ 5.5	50.4 $\pm$ 21.4	231 $\pm$ 41.2

<sup>1</sup>  $M \pm \sigma$  is the mean effect  $\pm$  its standard deviation.

over a period of about 10 days until they could consistently recognize the normal end point. The end point used in this work was the same as that described by Hardy, Wolff and Goodell (3). Provided the end point is well defined in the mind of each volunteer the results obtained are remarkably consistent.

Table 1 summarizes the results of the experiments regarding the analgetic potency of the three new agents with respect to morphine on subcutaneous injection. The results of this study indicate the following: 1. That, in general, the peak effect is reached sooner with the three new agents than with morphine at the same milligram dose. 2. When compared on a milligram dosage basis (above 5 mg.) the relative potencies stand in the following order: morphine, Nu-1779, Nu-1932, Nu-1196. Nu-1932 in a 1 to 5 mg. dosage stands highest in this series. 3. The heights of peaks pro-

gressively increased with dosage in the case of Nu-1779 and Nu-1196, and morphine. In the instance of Nu-1932, this drug apparently reaches a ceiling effect at a dose of about 2.5 mg. 4. The variability of Nu-1196 and Nu-1779 with regard to height of peak, time to reach peak and duration were of the same order as that of morphine. Nu-1932, on the other hand, shows considerable variability in all these respects. 5. It was interesting to note

TABLE 2. COMPARISON OF PEAK HEIGHT AND TIME TO REACH PEAK WITH ORAL AND SUBCUTANEOUS ADMINISTRATION

DRUG	DOSE	M <sup>1</sup> -PEAK ORAL	M <sup>1</sup> -PEAK SUBCUT.	M <sup>1</sup> -TIME TO REACH PEAK—ORAL	M <sup>1</sup> -TIME TO REACH PEAK SUBCUT.
	mg.			min.	min.
Nu-1196. ....	10	15.3	17.2	84	57.5
Nu-1779. ....	10	20.9	17.8	120	65.0

<sup>1</sup> M = mean.

that the duration was found in all cases to be approximately directly proportional to the peak.

Table 2 summarizes the comparisons of peak height and time to reach peak with regard to oral and subcutaneous routes of administration of the two drugs Nu-1196 and Nu-1779. In this case no great difference in peak height was observed between subcutaneous and oral routes of administration, but the time to reach the peak effect was markedly increased by oral

TABLE 3. COMPARATIVE SIDE EFFECT RATING AT VARIOUS LEVELS

	5 MG.	10 MG.	15 MG.
Morphine SO <sub>4</sub> . ....	82	161	252
Nu-1779. ....	134	192	312
Nu-1196. ....	30	49	103
Nu-1932. ....	33	88	188

The figures given in this table were obtained by multiplying number rating times the number of plus signs (+) and totaling all such products for the given drug at the given dose.

administration. The fact that the eventual peak obtained in oral administration was comparable with that by the subcutaneous route indicates very good adsorptions by the oral route.

Table 3 summarizes the data regarding side effects produced by the three new agents and morphine. This table was constructed in such a manner that the relative numbers given take into account both frequency and severity of all side effects observed. The manner in which these numbers were obtained is illustrated by table 4. The arrangement of the relative severity of the signs and symptoms as listed is purely arbitrary on our part.

TABLE 4. SIDE EFFECTS

NO. RATING	5 MG.				10 MG.				15 MG.			
	Morphine SO <sub>4</sub>	1196	1779	1932	Morphine SO <sub>4</sub>	1196	1779	1932	Morphine SO <sub>4</sub>	1196	1779	1932
19 Vomiting.....									2		2	
18 Dyspnea.....											1	
17 Nausea.....			3	1	2		3	2	3	2	3	3
16 Jumpiness, jitters.....											2	1
15 Dizziness.....	3	2	3		4	3	4	2	4	4	4	3
14 Chills.....												1
13 Itching.....			1		2		3		3		3	1
12 Urticaria at site.....									1			1
11 Pressure.....											1	
10 Sweating.....							1				1	
9 Thirsty, dry mouth.....			1				3				3	1
8 Sedation.....	4		2	2	4		3	3	4	1	3	3
7 Poor coordination.....									1			
6 Inability to concentrate.....											1	
5 Intestinal contractions.....	1				1				2		1	
4 Bad taste.....						1				1		
3 Tired but not sleepy.....												
2 Head full, heavy head.....									1			1
1 Neck stiff.....												1

<sup>1</sup> Indicates 0 to  $\frac{1}{4}$  of the group showed the given effect. <sup>2</sup> Indicates  $\frac{1}{4}$  to  $\frac{1}{2}$  showed the effect. <sup>3</sup> Indicates  $\frac{1}{2}$  to  $\frac{3}{4}$  showed the effect. <sup>4</sup> Indicates  $\frac{3}{4}$  to all showed the effect.

Table 5 indicates the comparative side effects produced by the three new agents and morphine at approximately the same analgetic level.

With respect to Nu-1196 and Nu-1779, blood pressure and pulse rates showed approximately the same alteration as morphine at the same milligram dosage level. Nu-1932 showed rather marked bradycardia in doses of 5 mg. and above, blood pressure alterations being similar to those produced by the other agents.

In view of the fact that Nu-1196 showed the least undesirable side effects even in relatively high dosage more extensive studies were conducted

TABLE 5. COMPARATIVE SIDE EFFECT RATING AT SAME ANALGETIC LEVEL

	DOSE	SIDE EFFECT RATING
	mg.	
Morphine SO <sub>4</sub> .....	10	161
Nu-1779.....	10	192
Nu-1196.....	15	103
Nu-1932.....	5	33

These figures were obtained in the same manner as those of table 3.

with this drug than with Nu-1779 and Nu-1932. To this end Nu-1196 was compared with regard to peak, average time to reach peak, and average duration of action following various routes of administration and with co-medication. Tables 6 and 7 summarize these results. With intravenous administration the peak is higher and duration shorter than by the other routes of administration. Table 7 points out the effect of premedication with atropine and indicates that while the peak effect is not materially altered the duration is shortened.

TABLE 6. COMPARISON OF VARIOUS ROUTES OF ADMINISTRATION OF 1196

DOSE	ROUTE	AVERAGE PEAK % RISE	AVERAGE TIME TO REACH PEAK	AVERAGE DURATION
mg.			min.	min.
10	I.V.	25.0	20.0	97
10	S.C.	17.2	57.5	190
10	<sup>1</sup>	15.3	84.0	220

<sup>1</sup> Orally on empty stomach.

Two subjects receiving 40 mg. of Nu-1196 daily in divided oral doses for nine days showed no material alteration in analgesia (peak or duration) or any change in daily W.B.C. and R.B.C.

The data presented in the various tables clearly demonstrate that these three new compounds are potent analgesic agents. It must be pointed out, however, in the light of experiments carried out on other animals (2), that there is a great species difference in analgesic potency. In our experiments only Nu-1932 was more potent than morphine and this only occurred up to

TABLE 7. EFFECT OF CO-MEDICATION ON THE ANALGESIA BY 1196

DOSE	ROUTE	% RISE AVER- AGE PEAK	AVERAGE DURATION
			min.
8 cases 10 mg. alone.....	S.C.	17.2	191
4 cases 10 mg. + 0.5 mg. atropine, .....	S.C.	18.5	88

the 5 mg. level. Both Nu-1196 and Nu-1779 were less potent than morphine in our human subjects. Randall and Lehmann using rats found equal efficiency for Nu-1196 and much greater efficiency for Nu-1779 and Nu-1932. The drug Nu-1779, while it exerts a potency in the general range of morphine, produces a higher degree of undesirable side effects, especially nausea, vomiting and respiratory depression. That the respiratory depression is a real depression has been confirmed by the department of anesthesiology in some preliminary clinical trials using this agent for premedica-

tion (4). While the drug Nu-1932 has a fairly high degree of potency in the lower dosage range, the fact that it shows a great variability with regard to peak and time to reach peak makes its use too unreliable for predictable clinical development. In addition it reveals a ceiling effect at doses far below highly effective analgesic levels.

The drug Nu-1196 appears to be the most promising member of this group of drugs from its clinical adaptability. Its low incidence of side effects make it appear that much larger doses than the ones we have used experimentally may be employed. Its main side effect appears to be dizziness and slight nausea. This drug, in our opinion, deserves clinical trial.

#### SUMMARY

Three new piperidine derivatives Nu-1196, Nu-1779 and Nu-1932 were studied for analgesic potency in normal human subjects. All of these drugs may be classified as potent analgesic agents. Nu-1196, while being the least potent on a milligram dosage basis, shows the greatest clinical promise, since at comparable analgetic levels its side effects are minimal relative to the other two agents and morphine.

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# *Arterial Blood Gases and Acid-Base Balance at Sea Level and at High Altitudes*

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IT HAS BEEN DEMONSTRATED that a low pressure environment has a definite influence on the gas content and acid-base balance of the arterial blood.

The length of the exposure and the level of pressure are important factors in determining the variability of the changes which take place. However, there are in the literature very few observations on people living permanently at high altitudes, in a condition of chronic anoxia, whose characteristics may furnish the necessary understanding of the nature of adaptation to this environment. Such data are also important, on a comparative basis, to rate the degree of acclimatization in people who are subjected temporarily to this condition.

The investigations reported in this paper have been made in residents at sea level and in Indian natives, born and raised at high altitudes and living permanently in different localities in the Andean region. Studies have also been carried out on newcomers at high altitudes, within the first two hours after arrival. Some of the previous reported and related observations have been reviewed and compared with our findings, but no attempt has been made to include the vast literature accumulated in this field (1).

## METHODS

Arterial blood was obtained anaerobically from the radial artery. A solution of heparin (Connaught) was used as anticoagulant. The blood samples were kept under mercury and in ice until the analyses were made; the time that elapsed between puncture and analysis varied between a few minutes and six hours. The gas analyses were made in the Van Slyke manometric apparatus.

The acid-base balance was determined according to the techniques developed at the Fatigue Laboratory (Harvard University, 2); the  $\text{CO}_2$  and  $\text{O}_2$  content of the blood as drawn and of that equilibrated in a tonometer at  $\text{pCO}_2 = 40$  mm. Hg and  $\text{pO}_2$  of about 200 mm. Hg gave the oxygen

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saturation and one point ( $T_{10}$ ) on the  $\text{CO}_2$  dissociation curve. From these figures, and by means of graphic methods (2), the  $(\text{pCO}_2)_b$ ,  $(\text{CO}_2)_s$ ,  $(\text{H}_2\text{CO}_3)_s$  and the  $(\text{BHCO}_3)_s$  were calculated.  $\text{pH}_s$  was given by the Henderson-Hasselbalch formula:  $\text{pH}_s = 6.11 + \log (\text{BHCO}_3)_s - \log (\text{H}_2\text{CO}_3)_s$ . The equilibration in the tonometer was carried out for a period of 20 minutes in a water bath at  $37^\circ\text{C}$ . The tonometer gas mixture was analyzed in the Haldane-Henderson apparatus.

Table 1 gives the altitudes of the different localities in the Andean region where the observations were carried out. Studies were also made

TABLE 1. PLACES ON THE ANDEAN WESTERN SLOPES WHERE THE OBSERVATIONS REPORTED IN THIS PAPER WERE CARRIED OUT

PLACES	ALTITUDE		AV. BAROM. PRESS., MM. HG
	Meters	Feet	
Lima.....	Sea level <sup>1</sup>	Sea level	753
Matucana.....	2,390	7,920	581
San Mateo.....	3,140	10,300	531
Oroya.....	3,730	12,240	482
Casapalca.....	4,165	13,660	468
Morococha.....	4,540	14,900	448
La Cima.....	4,835	15,860	432
Nicolas.....	4,860	15,940	429

Some observations were also made during a flight, immediately after the plane reached an altitude of 5740 meters (18,830 feet).

<sup>1</sup> Lima is located at an altitude of 150 meters (490 feet) and may be considered as sea level from the point of view of the observations made.

during a flight after the plane reached an altitude of 5740 meters (18,830 feet). All men studied were healthy adult males, of an age ranging from 18 to 38 years. The subjects at sea level and those studied after arrival at high altitudes were medical students, of white and mixed races; those living in the high places were of the Indian race, of about the same age, born in the localities where they were studied or in near-by places. Special precautions were taken to exclude possible cases of pneumoconiosis, a disease prevalent in the mining towns of the Andean zone. All the observations on the acid-base balance were made in blood taken in the fasting condition.

## RESULTS

*Arterial Gas Content and Oxygen Saturation.* Table 2 contains the values obtained for the arterial  $\text{CO}_2$  content,  $\text{O}_2$  content, capacity and saturation in 38 residents at sea level and in different groups of men, 68 in all, living permanently at the altitudes of 2390 meters (7840 feet), 3140 meters (10,300 feet), 3730 meters (12,230 feet), 4540 meters (14,900 feet) and 4860 meters (15,940 feet).



The  $\text{CO}_2$  content, which at sea level had a mean value of  $45.68 \pm 0.34$  vol. per cent, dropped gradually in a linear relationship to the level of altitude, reaching a value of  $33.95 \pm 0.37$  vol. per cent at the highest place. The decrease averaged 2.4 vol. per cent per each thousand meters. The mean  $\text{HbO}_2$  content of  $20.74 \pm 0.21$  vol. per cent at sea level showed a rise at high altitudes; the mean value of  $23.41 \pm 0.42$  vol. per cent found in San Nicolás, at 4860 meters of altitude, indicated that in men living at this

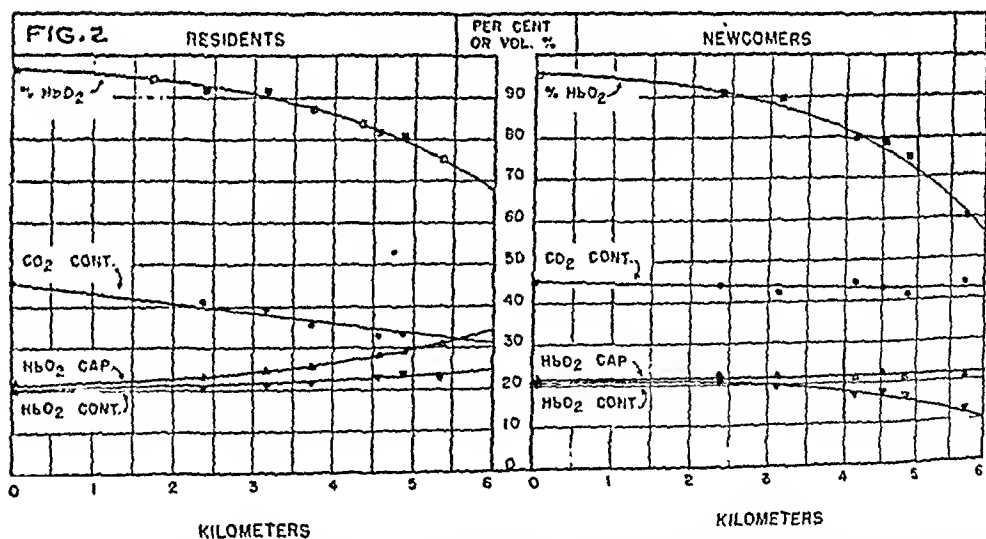
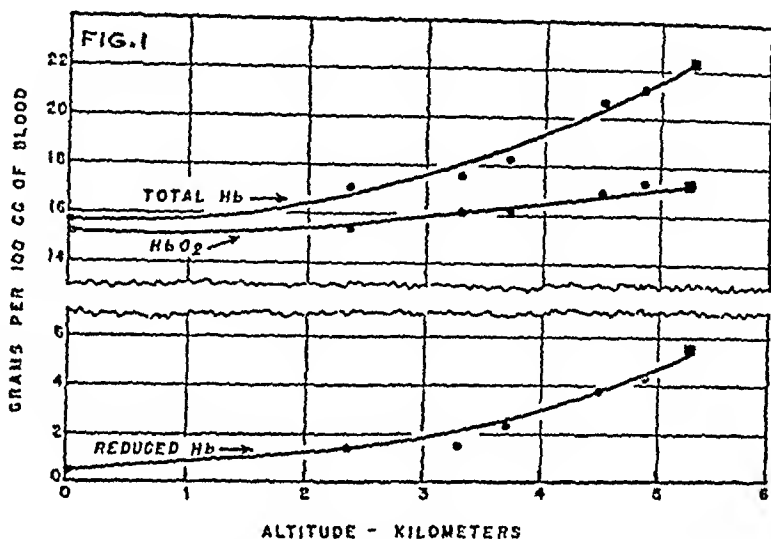


Fig. 1. TOTAL Hb, HbO<sub>2</sub> and reduced Hb, in gm/100 cc. of arterial blood, in permanent residents at high altitudes. Each circle represents the mean value found in a locality on the Andean region. The highest value (solid square) has been calculated from the data of Dill, Christensen and Edwards (3).

Fig. 2. COMPARATIVE STUDY of the mean values for percentage of HbO<sub>2</sub>, CO<sub>2</sub> content, HbO<sub>2</sub> capacity and content (vol. %) found in permanent residents at various altitudes with those observed in newcomers, studied within the first two hours after arrival. Solid circles, squares and triangles correspond to our observations; empty squares in the curve of percentage of HbO<sub>2</sub> (residents) have been taken from the data of Stammers (4), Barcroft *et al.* (5) and Dill, Christensen and Edwards (3).

altitude there is carried from the lungs to the tissues, in each 100 cc. of blood, an average of 2.67 cc. of oxygen more than at sea level, in spite of the marked decrease in the percentage saturation with this gas.

The HbO<sub>2</sub> capacity of the blood showed a definite increase in residents at high altitudes; the ascending curve, in relation to the level of altitude, showed a steeper rise above 3000 meters, but the greater capacity for oxygen was also evident at the lower altitude (2390 meters) where it had a value of  $23.14 \pm 0.58$  vol. per cent as compared with  $21.66 \pm 0.21$  at sea level. At the highest place (4860 meters) the oxygen capacity was  $29.04 \pm 0.58$  vol. per cent. In percentages, the increases in these two altitudes corresponded to 6.8 and 34.1 per cent over the sea level value.

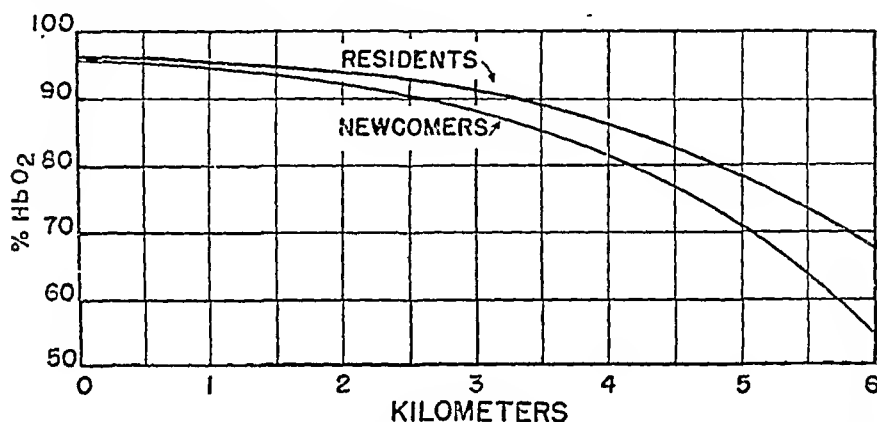


Fig. 3. ARTERIAL OXYGEN SATURATION, in relation to the level of altitude, in permanent residents at high altitudes and in newcomers, studied within the first two hours after arrival. Curves have been constructed from the data contained in tables 2 and 3.

The oxygen saturation fell gradually with increasing altitudes, but the drop became more marked above 3000 meters. From the mean value of  $96.1 \pm 0.18$  per cent at sea level it decreased to  $91.0 \pm 0.59$  per cent in San Mateo, at 3140 meters; at approximately 1700 meters higher (San Nicolás, 4860 meters) the mean saturation was found to be  $80.7 \pm 0.92$  per cent. Judging from the coefficients of variation of the values corresponding to each altitude, the range of variation in the percentage of HbO<sub>2</sub> was greater at the highest places; at sea level the coefficient of variation was 1.1 per cent, while in Morococha at 4540 meters and in San Nicolás at 4860 meters, it was 3.4 and 3.6 per cent, respectively.

Figure 1 shows the amount of total Hb, HbO<sub>2</sub> and reduced Hb, in gm/100 cc. of arterial blood, in residents at high localities, and in relation to the level of altitude. The curves have been constructed taking into account the oxygen capacity and the percentage saturation in the different places.

TABLE 2. OBSERVATIONS ON ARTERIAL BLOOD GASES IN RESIDENTS AT SEA LEVEL AND AT HIGH ALTITUDES

PLACE .....	LIMA	MIATUCANA	SAN MATEO	OROYA	MOROCOCHA	SAN NICOLÁS
Altitude, (m.) .....	Sea level	2390	3140	3730	4540	4860
Av. bar. Press., mm. Hg.	752	581	531	482	448	429
No. of subjects .....	38	12	11	15	18	12
CO <sub>2</sub> content, vol. %						
Mean $\pm$ S.E. ....	45.68 $\pm$ 0.34	41.07 $\pm$ 0.56	39.28 $\pm$ 0.71	36.02 $\pm$ 0.36	33.50 $\pm$ 0.18	33.95 $\pm$ 0.37
S.D. $\pm$ S.E. ....	2.06 $\pm$ 0.24	1.85 $\pm$ 0.40	2.27 $\pm$ 0.50	1.31 $\pm$ 0.24	0.76 $\pm$ 0.12	1.26 $\pm$ 0.47
Coef. of var. (%) ....	4.5	4.6	5.8	3.6	2.3	3.7
Extreme variations ...	40.68-48.79	37.99-43.42	36.36-41.95	33.98-37.79	31.86-37.73	32.48-36.29
HbO <sub>2</sub> content, vol. %						
Mean $\pm$ S.E. ....	20.74 $\pm$ 0.21	21.22 $\pm$ 0.38	21.87 $\pm$ 0.43	21.90 $\pm$ 0.39	23.00 $\pm$ 0.42	23.41 $\pm$ 0.43
S.D. $\pm$ S.E. ....	1.32 $\pm$ 0.15	1.30 $\pm$ 0.27	1.39 $\pm$ 0.31	1.47 $\pm$ 0.27	1.77 $\pm$ 0.30	1.41 $\pm$ 0.50
Coef. of var. (%) ....	6.4	6.1	6.3	6.7	7.7	6.0
Extreme variations ...	17.97-23.28	18.95-23.31	18.55-23.48	19.09-24.33	19.75-26.86	20.20-25.59
HbO <sub>2</sub> capacity, vol. %						
Mean $\pm$ S.E. ....	21.66 $\pm$ 0.21	23.14 $\pm$ 0.58	24.00 $\pm$ 0.33	24.07 $\pm$ 0.43	28.33 $\pm$ 0.49	29.04 $\pm$ 0.58
S.D. $\pm$ S.E. ....	1.32 $\pm$ 0.15	1.93 $\pm$ 0.42	1.02 $\pm$ 0.22	1.64 $\pm$ 0.31	2.08 $\pm$ 0.34	1.91 $\pm$ 0.43
Coef. of var. (%) ....	6.1	8.3	4.2	6.6	7.3	6.6
Extreme variations ...	18.76-24.22	20.56-25.12	21.34-26.12	22.61-28.38	24.49-32.79	26.88-33.51
% H <sub>2</sub> O <sub>2</sub>						
Mean $\pm$ S.E. ....	96.1 $\pm$ 0.18	91.7 $\pm$ 0.73	91.0 $\pm$ 0.59	87.6 $\pm$ 0.40	81.4 $\pm$ 0.67	80.7 $\pm$ 0.92
S.D. $\pm$ S.E. ....	1.1 $\pm$ 0.12	2.4 $\pm$ 0.50	1.9 $\pm$ 0.42	1.5 $\pm$ 0.28	2.8 $\pm$ 0.45	2.0 $\pm$ 0.65
Coef. of var. (%) ....	1.1	2.6	2.1	1.7	3.4	3.6
Extreme variations ...	93.9-98.6	88.4-95.4	86.9-93.2	84.4-90.2	75.2-86.2	75.1-84.5

There is a definite and gradual increase over the sea level value, as the altitude becomes higher, but the rate of the increase is more accentuated above 3000 meters, especially in regards to the quantity of total and reduced Hb.

Table 3 gives the values for the gas content and oxygen saturation of the arterial blood in different groups of people, 42 in all, habitual residents at sea level, who were studied within the first two hours after arrival to the altitudes of 2390 meters (7840 feet), 3140 meters (10,300 feet), 4165 meters (13,660 feet), 4540 meters (14,900 feet), 4835 meters (15,860 feet) and 5740 meters (18,830 feet). This last altitude was reached in a plane. The time of ascent from sea level to these different altitudes varied between one and three and a half hours; the ascent in the plane was accomplished in 30 minutes. All the subjects were in resting condition during the ascent and after arrival, previous to the time when the blood sample was obtained.

In the groups of newcomers at the high-altitude localities the CO<sub>2</sub> content showed a very insignificant tendency to decrease from the sea-level value, without a proportional relationship to the level of the altitude, except at the highest place (La Cima, 4835 meters), where its mean value was significantly lower than the one observed at sea level. It was interesting to find that the group of men studied in the plane, at 5740 meters, had practically no decrease. This seems to indicate that the early and slight reduc-

tion in the arterial  $\text{CO}_2$  content, which takes place in the first few hours after arrival to high altitudes, is more related to the actual time of exposure rather than to the level of altitude; thus the men in the plane, who reached a considerable height in only 30 minutes, had a higher  $\text{CO}_2$  content than the men who arrived at lower altitudes in a more prolonged time of ascent.

The  $\text{HbO}_2$  content decreased markedly and the reduction became evident at the lowest place (Matucana, 2390 meters), although this change

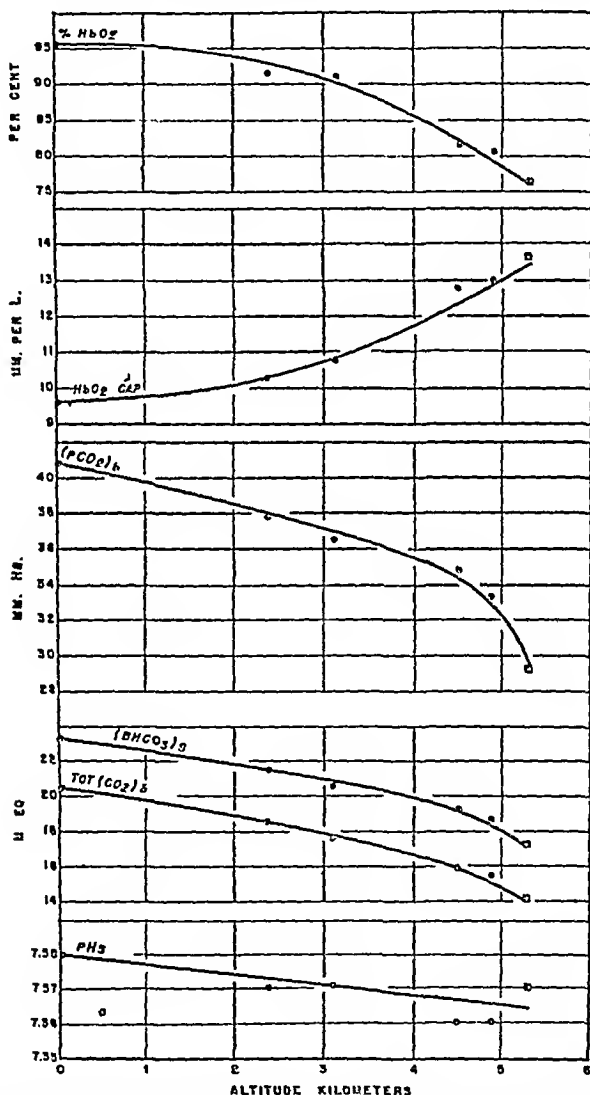


Fig. 4. PROPERTIES OF ARTERIAL BLOOD in permanent residents at sea level and at high altitudes. Each solid dot corresponds to a mean value obtained by us (table 5); the solid square at an altitude of 5340 meters has been calculated from the observations made by the High Altitudes Expedition to Chile (3, 6).

had a greater degree of accentuation in places located over the level of 3000 meters. In the plane, at an altitude of 5740 meters, the mean oxygen content in the arterial blood was  $12.89 \pm 0.43$  cc. per 100 cc. in contrast to  $20.74 \pm 0.21$  found in the residents at sea level. The  $\text{HbO}_2$  capacity did not present significant changes from the values observed at sea level. The percentage of  $\text{HbO}_2$  decreased on arrival to all altitudes, and this decrease also became especially accentuated and with a more rapid rate of descent over the level of 3000 meters.

Figure 2 shows graphically the mean values of the gas content and oxygen saturation of the arterial blood, in relation to the level of altitude,

TABLE 3. OBSERVATIONS ON THE ARTERIAL BLOOD GASES IN NEWCOMERS AT HIGH ALTITUDES (WITHIN THE FIRST TWO HOURS AFTER ARRIVAL)

PLACE .....	MATUCANA	SAN MATEO	CASAPALCA	MOROCOCHA	LA CIMA	PLANEZ
Altitude (m) .....	2390	3140	4165	4540	4835	5740
Av. bar. press., mm. Hg.	581	531	468	448	432	380
No. of subjects .....	5	5	5	15	7	5
<hr/>						
$\text{CO}_2$ content, vol. %						
Mean $\pm$ S.E. ....	$44.71 \pm 0.76$	$42.16 \pm 0.74$	$44.65 \pm 1.01$	$43.25 \pm 0.56$	$41.42 \pm 0.49$	$44.23 \pm 0.86$
S.D. $\pm$ S.E. ....	$1.51 \pm 0.53$	$1.50 \pm 0.53$	$2.07 \pm 0.73$	$2.19 \pm 0.40$	$1.19 \pm 0.34$	$1.73 \pm 0.61$
Coef. of var. (%) ....	3.4	3.5	4.6	5.1	2.9	3.0
Extreme variations...	42.79-46.60	39.58-43.60	42.45-48.52	39.28-47.76	40.01-43.99	42.39-47.13
$\text{HbO}_2$ content, vol. %						
Mean $\pm$ S.E. ....	$20.63 \pm 0.30$	$19.65 \pm 0.68$	$17.33 \pm 0.52$	$17.63 \pm 0.42$	$16.52 \pm 0.40$	$12.89 \pm 0.43$
S.D. $\pm$ S.E. ....	$0.60 \pm 0.21$	$1.37 \pm 0.49$	$1.04 \pm 0.37$	$1.60 \pm 0.30$	$1.00 \pm 0.28$	$0.87 \pm 0.31$
Coef. of var. (%) ....	2.9	7.0	6.0	9.1	6.1	6.7
Extreme variations...	19.02-21.58	18.22-22.03	15.04-18.70	15.41-20.45	14.52-17.68	11.77-14.16
$\text{HbO}_2$ capacity, vol. %						
Mean $\pm$ S.E. ....	$22.54 \pm 0.40$	$21.94 \pm 0.67$	$21.59 \pm 0.56$	$22.23 \pm 0.37$	$21.59 \pm 0.55$	$21.26 \pm 0.43$
S.D. $\pm$ S.E. ....	$0.81 \pm 0.28$	$1.33 \pm 0.47$	$1.12 \pm 0.40$	$1.45 \pm 0.27$	$1.36 \pm 0.39$	$0.86 \pm 0.31$
Coef. of var. (%) ....	3.6	6.1	5.2	6.5	6.3	4.0
Extreme variations...	21.28-23.71	20.02-23.82	19.82-22.58	19.06-24.89	19.79-23.48	20.47-22.91
% $\text{HbO}_2$						
Mean $\pm$ S.E. ....	$91.0 \pm 0.85$	$89.6 \pm 1.10$	$80.2 \pm 1.14$	$78.9 \pm 1.01$	$75.3 \pm 1.38$	$60.7 \pm 1.94$
S.D. $\pm$ S.E. ....	$1.7 \pm 0.59$	$2.2 \pm 0.77$	$2.30 \pm 0.82$	$3.9 \pm 0.71$	$3.4 \pm 0.98$	$3.0 \pm 1.38$
Coef. of var. (%) ....	1.9	2.5	2.9	4.9	4.5	6.4
Extreme variations...	88.2-93.6	86.2-92.5	77.0-83.2	70.7-83.8	70.4-79.8	56.7-66.8

in both groups studied—permanent residents and newcomers. This comparative study reveals that men living permanently at high altitudes have, as compared with newcomers (studied within the first two hours after arrival), a lower  $\text{CO}_2$  content and a higher  $\text{HbO}_2$  content, capacity and percentage saturation. This last characteristic has a special interest; it means that the man who has just arrived to a high altitude is subject to a more marked degree of anoxemia than the man living constantly in this environment. Figure 3 shows in a greater detail the difference between the two subjects. While the permanent resident has an arterial oxygen saturation of 90 per cent at an altitude of about 3300 meters, the same degree

of anoxemia is present in the newcomer at about 2600 meters. However, it must be emphasized that according to our observations the discrepancy observed in the two groups is especially definite and significant at high rather than at low levels.

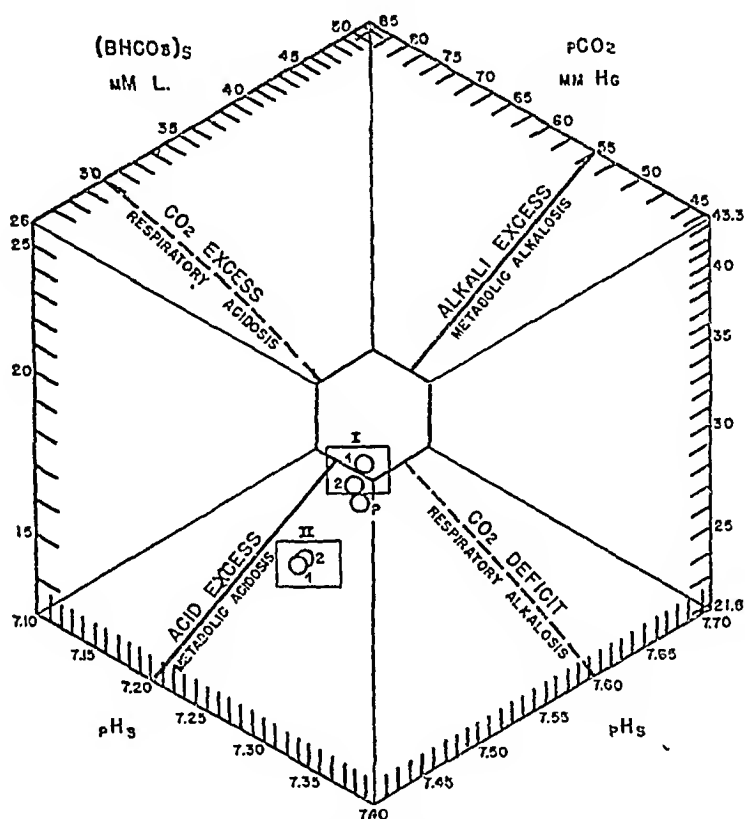


Fig. 5. TRIAXIAL COORDINATES DIAGRAM of Shock and Hastings (7) for the graphic representation of the acid-base balance of the blood. Central hexagon is the normal zone at sea level. *Area I:* circle 1 corresponds to the acid-base balance in 15 men residents at sea level; circle 2 is the same group within the first two hours after arrival to an altitude of 4540 meters (table 6). Circle P represents the acid-base balance of a group of men studied during a flight at an altitude of 5740 meters (table 7); no previous observations were made at sea level. *Area II:* circle 1 corresponds to the acid-base balance in a group of 8 men permanent residents at 4540 meters of altitude; circle 2 is the same group immediately after arrival at sea level (table 8).

Eight of the permanent residents of Morococha, at 4540 meters, were brought down to Lima, at sea level, and studied within the first two hours after arrival. Table 4 contains the results obtained. In most of the subjects the  $\text{CO}_2$  content showed a slight rise, the  $\text{HbO}_2$  content increased from a mean value of 24.64 vol. per cent at high altitudes to 28.38 vol. per cent at sea level, and the  $\text{HbO}$  capacity practically did not vary. The percentage of  $\text{HbO}_2$  increased in all subjects but it was noteworthy that in four of

them the degree of oxygen saturation was, on arrival at sea level, slightly below the lower limit of normal variation.

*Acid-base Balance of the Blood.* Table 5 shows the results obtained in the determinations of the acid-base balance of the arterial blood in 37 residents at sea level and in 48 Indian natives, born and raised at high altitudes and living permanently in the following localities on the Andean region: Matucana (2390 meters, 7840 feet), San Mateo (3140 meters, 10,300 feet), Morococha (4540 meters, 14,900 feet) and San Nicolás (4860

TABLE 4. OBSERVATIONS ON THE ARTERIAL BLOOD GASES IN NATIVE RESIDENTS AT MOROCOCHA (AT 4540 METERS OF ALTITUDE) AND IMMEDIATELY AFTER ARRIVAL AT SEA LEVEL

SUBJECTS	CO <sub>2</sub> CONT. vol. %		HbO <sub>2</sub> CONT. vol. %		HbO <sub>2</sub> CAP. vol. %		% HbO <sub>2</sub>	
	H.A.	S.L.	H.A.	S.L.	H.A.	S.L.	H.A.	S.L.
1	35.41	32.85	25.56	32.00	33.71	34.48	75.8	91.5
2	33.96	35.81	24.79	26.99	29.52	29.17	84.0	92.5
3	35.13	35.43	24.24	28.84	30.68	29.72	79.0	97.0
4	34.97	35.07	22.97	24.26	26.85	25.29	85.5	95.9
5	32.71	33.36	24.58	27.82	29.96	30.12	82.0	92.4
6	37.73	38.08	23.51	27.10	30.69	29.08	76.6	93.2
7	36.97	37.00	26.86	31.55	32.79	32.54	81.9	96.9
8	36.66	32.62	24.64	28.45	29.24	29.28	84.3	97.2
Mean...	35.44	35.03	24.64	28.38	30.43	29.96	81.1	94.6

meters, 15,940 feet). Figure 4 gives graphically the relationship of the mean observed chemical characteristics, related to the acid-base balance, to the level of altitude.

The mean values for (Tot. CO<sub>2</sub>)<sub>b</sub>, (pCO<sub>2</sub>)<sub>b</sub> and (BHCO<sub>3</sub>)<sub>s</sub> showed a definite decrease at high altitudes and, according to figure 4, the degree of reduction had a linear relationship to the level of altitude up to about 5000 meters, where the decrease became more marked. From a mean value of  $40.8 \pm 0.46$  mm. Hg, at sea level, the (pCO<sub>2</sub>)<sub>b</sub> fell to  $33.0 \pm 0.70$  at an altitude of 4860 meters. In relation to the altitude this variation meant a drop of approximately 1.6 mm. Hg per thousand meters. The alkaline reserve, in terms of (BHCO<sub>3</sub>)<sub>s</sub>, (Tot. CO<sub>2</sub>)<sub>s</sub> or (Tot. CO<sub>2</sub>)<sub>b</sub> in oxygenated blood at pCO<sub>2</sub> = 40 mm. Hg (T<sub>40</sub>), also showed a progressive fall as the altitude became greater. From a sea level mean value of  $23.64 \pm 0.16$  mEq. the (BHCO<sub>3</sub>)<sub>s</sub> dropped to  $18.53 \pm 0.18$  at 4860 meters, equivalent to a reduction of 1.05 mEq. per thousand meters. The (Tot. CO<sub>2</sub>)<sub>s</sub> decreased from  $25.08 \pm 0.16$  mEq. at sea level to  $19.57 \pm 0.16$  at the above altitude and T<sub>40</sub> from  $20.25 \pm 0.13$  mEq. to  $16.26 \pm 0.16$ . In terms of altitude these reductions were equivalent to 1.14 and 0.83 mEq. per each

kilometer, respectively. From the study of figure 4 it appears that the values just given for the average decreases per each thousand meters do not hold for altitudes over 5000 meters, because at this high level the further reductions of  $(pCO_2)_b$  and the alkaline reserve no longer follow a linear relationship to the level of altitude.

The pHs was found to be within the normal limits of variation at all altitudes and in all the subjects studied. There was, however, some tendency for a slight decrease, but the observed differences did not have a statistical significance. At the two highest places the mean pHs was  $7.36 \pm 0.009$  as compared with  $7.38 \pm 0.004$  at sea level.

In order to study the early changes which might take place in the acid-base balance of the blood during exposure to a low pressure environment

TABLE 5. OBSERVATIONS ON THE ACID-BASE BALANCE (ARTERIAL BLOOD) IN RESIDENTS AT SEA LEVEL AND AT HIGH ALTITUDES

PLACE Altitude (m.) Av. bar. press., mm. Hg No. of subjects	LIMA Sea level 752 37	MATUCANA 2390 581 12	SAN MATEO 3140 531 11	MOROCOCHA 4540 448 13	SAN NICOLÁS 4860 429 12
(Tot. $CO_2$ ) <sub>b</sub> , mEq. Mean $\pm$ S.E. S.D. $\pm$ S.E. Coef. of var. (%) Extreme variations	$20.50 \pm 0.15$ $0.93 \pm 0.10$ 4.5 18.36-21.92	$18.45 \pm 0.25$ $0.84 \pm 0.18$ 4.6 17.07-19.51	$17.64 \pm 0.33$ $1.02 \pm 0.22$ 5.8 16.33-19.00	$15.85 \pm 0.19$ $0.69 \pm 0.13$ 4.3 14.69-16.95	$15.25 \pm 0.18$ $0.57 \pm 0.12$ 3.7 14.59-16.30
(p $CO_2$ ) <sub>b</sub> , mm. Hg Mean $\pm$ S.E. S.D. $\pm$ S.E. Coef. of var. (%) Extreme variations	$40.8 \pm 0.46$ $2.8 \pm 0.33$ 6.2 34.4-45.9	$37.8 \pm 0.53$ $1.8 \pm 0.38$ 4.8 34.9-40.4	$36.4 \pm 0.86$ $2.7 \pm 0.61$ 7.4 32.5-40.0	$34.7 \pm 0.73$ $2.5 \pm 0.50$ 7.2 31.8-39.8	$33.0 \pm 0.70$ $2.3 \pm 0.49$ 7.0 28.2-36.1
( $BHCO_3$ ) <sub>s</sub> , mEq. Mean $\pm$ S.E. S.D. $\pm$ S.E. Coef. of var. (%) Extreme variations	$23.64 \pm 0.16$ $1.01 \pm 0.12$ 4.3 21.21-25.40	$21.48 \pm 0.31$ $1.02 \pm 0.22$ 4.7 19.99-22.99	$20.71 \pm 0.33$ $1.05 \pm 0.24$ 5.1 19.17-22.33	$19.17 \pm 0.25$ $0.90 \pm 0.18$ 4.7 17.54-20.84	$18.53 \pm 0.18$ $0.60 \pm 0.13$ 3.2 17.74-19.55
pHs Mean $\pm$ S.E. S.D. $\pm$ S.E. Coef. of var. (%) Extreme variations	$7.38 \pm 0.004$ $0.03 \pm 0.003$ 0.4 7.32-7.46	$7.37 \pm 0.009$ $0.03 \pm 0.006$ 0.4 7.34-7.41	$7.37 \pm 0.003$ $0.01 \pm 0.002$ 0.1 7.34-7.40	$7.36 \pm 0.010$ $0.04 \pm 0.007$ 0.6 7.30-7.40	$7.36 \pm 0.009$ $0.03 \pm 0.006$ 0.4 7.34-7.42
Oxygen blood at $pCO_2 = 40$ mm. Hg					
(Tot. $CO_2$ ) <sub>b</sub> (T <sub>10</sub> ), mEq. Mean $\pm$ S.E. S.D. $\pm$ S.E. Coef. of var. (%) Extreme variations	$20.25 \pm 0.13$ $0.78 \pm 0.09$ 3.8 18.49-22.25	$18.69 \pm 0.19$ $0.63 \pm 0.13$ 3.4 17.39-19.68	$18.18 \pm 0.19$ $0.61 \pm 0.13$ 3.3 17.20-18.76	$16.45 \pm 0.22$ $0.77 \pm 0.16$ 4.7 15.03-17.25	$16.26 \pm 0.16$ $0.52 \pm 0.12$ 3.2 15.71-17.57
(Tot. $CO_2$ ) <sub>s</sub> , mEq. Mean $\pm$ S.E. S.D. $\pm$ S.E. Coef. of var. (%) Extreme variations	$25.08 \pm 0.16$ $1.01 \pm 0.12$ 4.0 22.36-26.63	$22.66 \pm 0.31$ $1.05 \pm 0.22$ 4.6 21.16-24.15	$21.86 \pm 0.30$ $0.93 \pm 0.21$ 4.3 20.27-23.58	$20.26 \pm 0.27$ $0.93 \pm 0.19$ 4.6 18.59-21.96	$19.57 \pm 0.16$ $0.66 \pm 0.10$ 3.4 18.84-20.68



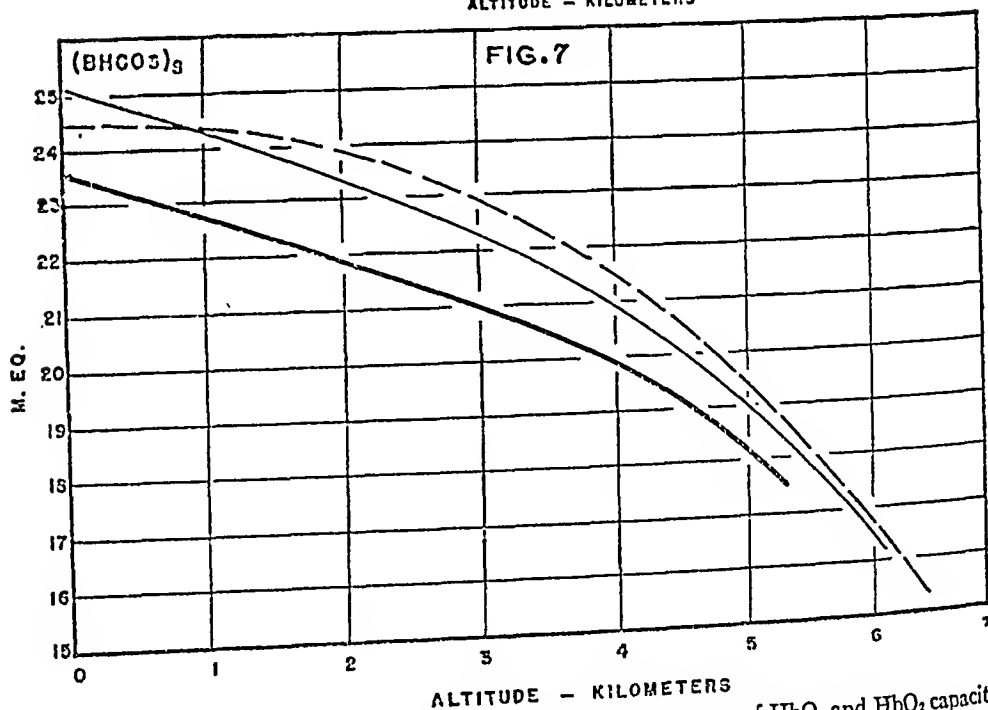
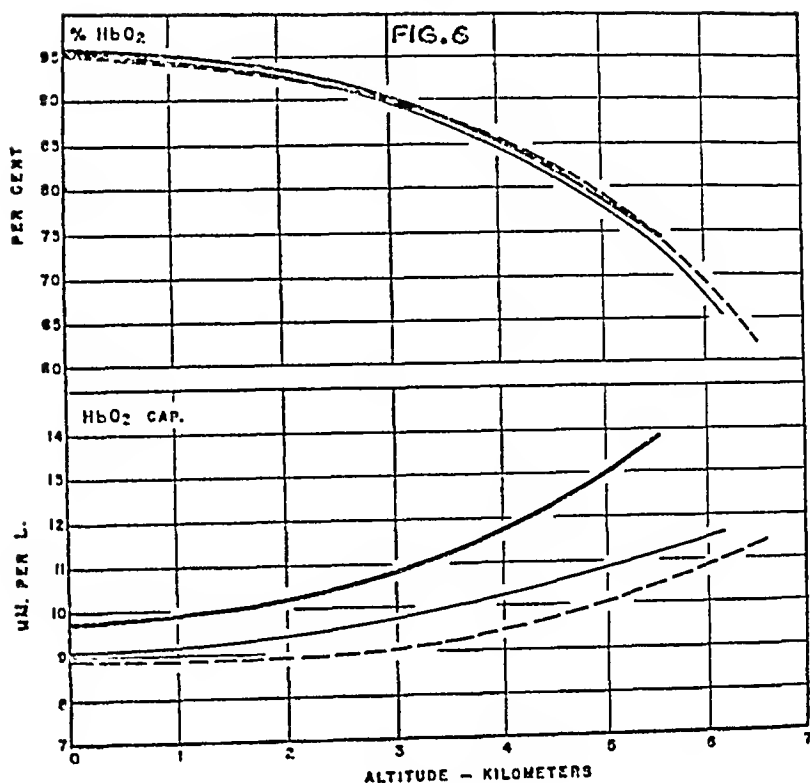


Fig. 6. COMPARATIVE STUDY of the mean values for percentage of HbO<sub>2</sub> and HbO<sub>2</sub> capacity in relation to the altitude level observed by us in the Indian native residents on the Andean zone (heavy continuous line) with those found in the party members of the High Altitudes Expedition to Chile during a period of 14 weeks of gradual ascent and residence at high altitudes (light continuous line) and in 4 subjects subjected for 4 weeks to a gradual ascent to simulated altitudes in a low-pressure chamber (interrupted line). The curves corresponding to these last two groups have been constructed by us on the basis of the data reported in the literature (3, 6, 22).

Fig. 7. COMPARATIVE STUDY, as explained in the legend of figure 6, except for the mean values of (BHC0<sub>3</sub>)<sub>s</sub>.

we took 15 men, residents in Lima, at sea level, to Morococha, at 4540 meters of altitude, where arterial blood was obtained within the first two hours after arrival. The findings were compared to those previously observed at sea level. The time of ascent from Lima to Morococha was approximately three and a half hours, and during this period and also after arrival all men were in resting condition. Table 6 contains the results of this investigation. There occurred a moderate drop in the  $(pCO_2)_b$  in

TABLE 6. OBSERVATIONS ON THE ACID-BASE BALANCE (ARTERIAL BLOOD AT SEA LEVEL AND WITHIN THE FIRST TWO HOURS AFTER ARRIVAL AT MOROCCHA AT 4540 METERS OF ALTITUDE)

SUBJECTS	$(\text{TOT. CO}_2)_b$ mEq.		$(pCO_2)_b$ mm. Hg		$(\text{BICARB})_s$ mEq.		pHs		OXYGEN. BLOOD AT $pCO_2 = 40$ mm. Hg			
									$(\text{Tot. CO}_2)_b$ mEq. (T40)		$(\text{Tot. CO}_2)_s$ mEq.	
	S.L.	H.A.	S.L.	H.A.	S.L.	H.A.	S.L.	H.A.	S.L.	H.A.	S.L.	H.A.
1	21.75	18.84	45.9	36.6	24.33	21.24	7.34	7.38	20.44	18.96	25.77	22.39
2	20.57	19.66	40.0	37.3	24.03	22.87	7.39	7.40	20.47	19.58	25.29	24.04
3	19.93	17.77	38.0	38.9	23.05	20.21	7.40	7.33	20.12	17.36	24.24	21.43
4	20.76	19.43	37.8	40.3	24.42	21.90	7.42	7.35	21.06	18.66	25.61	23.16
5	21.67	19.73	41.8	40.6	25.32	23.09	7.40	7.37	21.12	19.09	26.33	24.36
6	20.62	19.81	40.4	36.8	23.80	23.19	7.38	7.41	20.35	19.67	25.07	24.34
7	20.16	18.79	37.9	35.8	23.57	21.98	7.41	7.40	20.53	19.09	24.77	23.10
8	21.54	21.45	36.0	39.3	25.40	24.83	7.46	7.42	22.25	20.71	26.53	26.06
9	19.77	18.72	39.3	38.6	23.12	21.94	7.38	7.37	19.86	18.48	24.35	23.14
10	21.20	21.28	39.8	40.4	24.40	24.35	7.40	7.39	21.14	20.73	25.65	25.61
11	20.04	19.79	39.5	37.0	23.36	23.31	7.39	7.41	20.02	19.87	24.60	24.46
12	20.41	19.87	39.0	38.7	23.28	22.75	7.39	7.38	20.49	19.75	24.50	23.06
13	21.40	19.73	41.5	38.9	24.77	22.98	7.39	7.38	20.98	19.38	26.07	24.20
14	18.36	18.53	36.0	37.2	21.21	21.45	7.39	7.37	19.15	18.59	22.36	22.62
15	20.54	17.65	42.6	33.0	23.53	20.54	7.36	7.40	20.11	18.64	24.87	21.58
Mean...	20.58	19.40	39.7	38.0	23.84	22.44	7.39	7.38	20.54	19.24	25.07	23.63

eight of the subjects and a more marked one in two of them; the average reduction amounted to 1.7 mm. Hg. The alkaline reserve, expressed by  $T_{40}$ , decreased in all subjects; the reductions varied between 0.15 and 2.03 mEq., with an average value of 1.30 mEq. The mean value of 25.07 for  $(\text{Tot. CO}_2)_s$  at sea level dropped to 23.63 mEq. at high altitudes. The pHs did not show constant variations; in 10 of the subjects it decreased slightly and in five of them rose also very moderately; the highest and the lowest pHs observed at high altitudes were 7.42 and 7.33, respectively. The mean values found were 7.39 at sea level and 7.38 at the high place.

Another group of five sea level residents was taken in a plane to an altitude of 5740 meters and arterial blood was obtained within the first hour after reaching this level. The time of ascent was approximately half

in the literature up to that time. Quite recently, Henson and others (14), on the basis of oximeter readings taken after exposures of an hour or less to low oxygen tensions, concluded that the percentage of  $\text{HbO}_2$  corresponding to the second quarter hour of exposure is significantly lower than that given by the *Handbook* and, consequently, these authors have suggested a revision. A comparison of our mean percentage of  $\text{HbO}_2$  at different altitudes with the curve given in Chart B-4 of the *Handbook* indicates that the values corresponding to our groups of newcomers, observed within the first two

TABLE 7. OBSERVATIONS ON THE ACID-BASE BALANCE (ARTERIAL BLOOD) IN 5 HEALTHY ADULTS IMMEDIATELY AFTER ARRIVAL TO AN ALTITUDE OF 5740 METERS (BAROMETRIC PRESSURE = 380 MM. HG)

	(TOT. CO <sub>2</sub> )b mEq.	(PCO <sub>2</sub> )b mm. Hg	(BPCO <sub>2</sub> )s mEq.	pHs	OXYGEN, BLOOD AT PCO <sub>2</sub> = 40 MM. HG	
					(Tot. CO <sub>2</sub> )s (T <sub>40</sub> ) mEq.	(Tot. CO <sub>2</sub> )s mEq.
Mean $\pm$ S.E.....	19.87 $\pm$ 0.39	38.1 $\pm$ 1.69	22.68 $\pm$ 0.47	7.39 $\pm$ 0.015	19.13 $\pm$ 0.38	23.87 $\pm$ 0.49
S.D. $\pm$ S.E.....	0.78 $\pm$ 0.27	3.4 $\pm$ 1.20	0.95 $\pm$ 0.34	0.04 $\pm$ 0.013	0.79 $\pm$ 0.28	0.98 $\pm$ 0.34
Coeff. of var. (%).....	3.9	8.9	4.2	0.5	4.1	4.1
Extreme variations.....	19.04-21.17	33.0-41.7	21.52-24.22	7.33-7.45	17.92-20.20	22.82-25.46

hours after arrival to high altitudes, are located slightly below that curve, with a very close agreement in regard to its shape and direction. On the other hand, our mean findings of the percentage of  $\text{HbO}_2$  in native residents at high altitudes, and also those reported by Barcroft and others (5), at 4350 meters, and Dill *et al.* (3), at 5340 meters, lie very distinctly above the curve of the *Handbook* and are higher than the ones reported by Henson and others (14), especially at altitudes above 4000 meters.

All our observations have been carried out at altitudes over 2000 meters, and for this reason the part of the curve of the percentage of  $\text{HbO}_2$  corresponding to lower levels, in figures 2 and 3, may not be strictly accurate. From the shape of the oxygen dissociation curve, which is practically unchanged at high altitudes (15, 16), it must be expected that at altitudes below that level the degree of arterial oxygen saturation is changed very little. The observations of Verzar and Vögtli (17), who determined the percentage of  $\text{HbO}_2$  at altitudes of 1280 and 1880 meters, are in agreement with this consideration. However, Stammers (4), in the study of 10 men, residents at 1750 meters in South Africa, observed a range of variation (92.3 to 94.2%) lower than the one found in people living at sea level.

The values observed by us for the acid-base balance of the arterial blood in sea-level residents may be compared with those reported by Dill, Edwards and Consolazio (9), Shock and Hastings (18) and Dill *et al.* (19). The mean pHs of 7.38 is the same as the one corresponding to 106 observa-

tions made in Boston (19) and slightly below to 7.40 obtained in 39 determinations in capillary blood (18). Our mean value of 40.8 mm. Hg for  $(pCO_2)_b$  is practically similar to 41.0 mm. Hg observed in 12 men (9) but lower than 43.88 mm. Hg found by Shock and Hastings in capillary blood. The mean  $T_{40}$  in the Lima residents (at sea level) is about 6 per cent lower than the one found in large series of observations carried out in the United States (19). It is not possible to express whether this difference is due to technical factors or to climatic or racial characteristics. Dill *et al.* (19), from studies made on white and colored subjects, and from an analysis of the possible climatic influences over the properties of the arterial blood, concluded that these do not show a definite relation to climate or race.

The acid-base balance of the blood under the influence of a low oxygen tension in the inspired air has been repeatedly studied at high altitudes and in men and animals in low pressure chambers. Most of the results obtained in these investigations point out that in this condition the acid-base balance shifts to the alkaline side, due to the loss of  $CO_2$ , from hyperventilation, and a less proportional drop in the bicarbonate, unless the degree of anoxia is very severe and capable of producing a true asphyxia, which is usually associated with an acidosis process. However, a review of the literature reveals that the time of exposure to the low oxygen tension varies markedly in the reported observations and that very few investigations have been made in people living permanently or with a prolonged residence at high altitudes. It is with the last aspects that we are especially concerned.

The findings of Barcroft and others (5) in the Cerro de Pasco Expedition were not well defined; after a few weeks' residence at 4350 meters of altitude most of the members of the expedition showed a rise in the pHs, and in three native residents the values found were 7.21, 7.30 and 7.41. Monge and others (20) in 1928, using a colorimetric technique and in analysis made in venous blood, observed pHs of 7.45 to 7.48 in native and temporary residents at an altitude of 3730 meters in contrast with a mean value of 7.39 at sea level. Dill *et al.* (21), in observations made in venous blood at altitudes of approximately 3000 and 4300 meters, observed in the members of the party, after a few days' residence, a decrease in the alkaline reserve and a rise in the pHs of about 0.03 and 0.08 at the above altitudes, respectively. In residents at the lower place, the pHs was also 0.03 higher than the sea level value and the alkaline reserve ( $T_{40}$ ) was 18.80 mEq. as compared with 21.18 mEq. in the party members before ascent.

The High Altitude Expedition to the Andean region of Chile (3, 6) made numerous observations in the members of the party, after a few weeks of residence and a gradual ascent to an altitude of 6140 meters. Recently, Houston and Riley (22) carried out the interesting investigation of observing the changes which took place in a group of four men who in a period of

approximately 30 days were gradually taken from a sea level pressure to a simulated altitude of 6400 meters in a low pressure chamber. The comparative study of the findings in regard to the properties of the arterial blood, including the acid-base balance, in the subjects of these two investigations, who were exposed in the Andean region for a period of about 14 weeks and in the chamber for approximately 4 weeks to a low pressure environment, with those found by us in the permanent residents at high altitudes, has a special interest from the point of view of rating acclimatization in terms of adaptation—the first process as shown by the subjects

TABLE 8. OBSERVATIONS ON THE ACID-BASE BALANCE (ARTERIAL BLOOD) IN NATIVE RESIDENTS AT MOROCOCHA (AT 4540 METERS OF ALTITUDE) AND IMMEDIATELY AFTER THEIR ARRIVAL AT SEA LEVEL

SUBJECTS	(Tot. CO <sub>2</sub> )b mEq.		(pCO <sub>2</sub> )b mm. Hg		(BHCO <sub>3</sub> )s mEq.		pHs		OXYGEN. BLOOD AT PCO <sub>2</sub> = 40 mm. Hg			
									(Tot. CO <sub>2</sub> )b (T40) mEq.		(Tot. CO <sub>2</sub> )s mEq.	
	H.A.	S.L.	H.A.	S.L.	H.A.	S.L.	H.A.	S.L.	H.A.	S.L.	H.A.	S.L.
1	15.78	15.91	34.5	36.7	19.33	19.35	7.36	7.34	16.38	16.61	20.41	20.50
2	15.26	16.09	33.9	37.3	18.55	19.32	7.35	7.33	16.18	16.64	19.61	20.49
3	14.69	14.99	35.3	34.8	17.68	18.30	7.31	7.33	15.18	16.02	18.78	19.39
4	16.61	16.62	39.8	39.3	20.12	20.40	7.32	7.33	15.97	16.70	21.37	21.63
5	16.95	17.11	35.5	37.3	20.84	20.74	7.38	7.36	17.25	17.53	21.96	21.91
6	14.82	14.52	33.7	27.7	17.54	18.19	7.33	7.43	15.65	17.40	18.59	19.06
7	15.71	15.75	32.6	33.2	18.95	18.84	7.38	7.37	16.99	17.23	19.98	19.89
8	15.91	14.76	39.8	37.5	19.13	18.16	7.30	7.30	15.03	15.07	20.38	19.34
Mean...	15.72	15.72	35.6	35.5	19.02	19.16	7.34	7.35	16.08	16.65	20.14	20.28

exposed in a prolonged but temporary period and the second one found in the men born and raised under this condition. Figures 6, 7 and 8 give graphically the results of this comparative study. The degree of anoxemia, represented by the percentage of HbO<sub>2</sub> in the members of both parties, in Chile and in the chamber, was essentially the same as the one found in the native residents at all altitudes. On the other hand, the polycythemic response to the anoxic stimulus, given by the HbO<sub>2</sub> capacity, was quite different in the three groups—more marked in the native residents and least evident in the chamber subjects. The level in the Chilean party occupied an intermediate position. The difference between the native and the temporary residents was greater the higher the altitude (fig. 6). The acid-base balance characteristics showed definite variations; the (BHCO<sub>3</sub>)s was lowest in the permanent residents and highest in the chamber subjects, while the (pCO<sub>2</sub>)b had the inverse relationship, especially at the very high levels. The party members in Chile occupied again an inter-

mediate position (fig. 7 and 8). The pHs showed the most marked deviation to the alkaline reaction in the chamber group, contrasting with the slight tendency to its decrease in the native residents; the members of the Chilean Expedition also had a higher pHs than the residents, but the difference was of a lesser degree (fig. 8). In general, this comparative study shows that both groups, in Chile and in the chamber, did not reach the characteristics exhibited by the permanent residents, in spite of an exposure of several weeks and the existence of an anoxic stimulus of the same degree—the polycythemia level was lower and the acid-base balance had a definite shift to alkalinity during the temporary exposure.

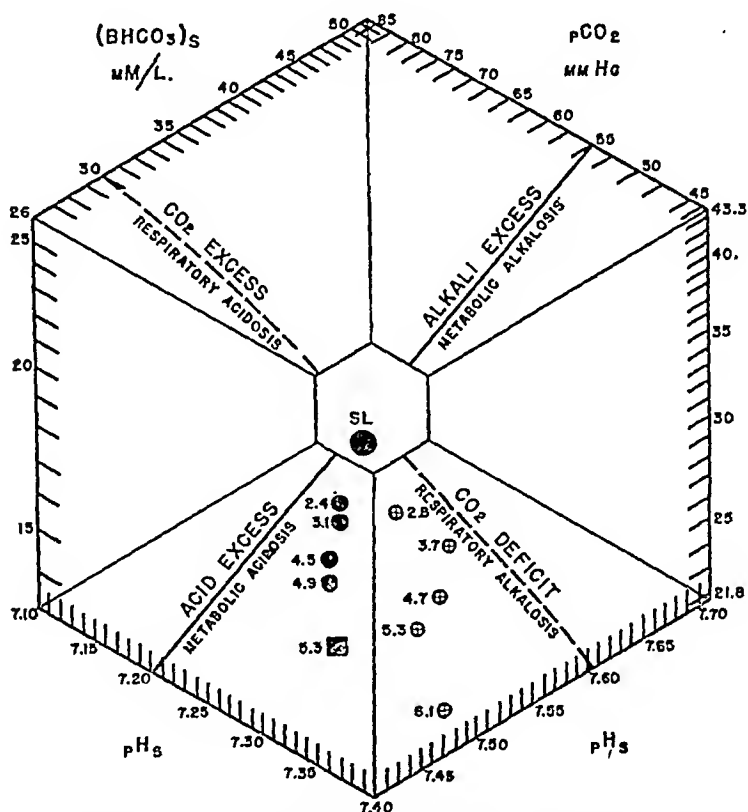


Fig. 9. POSITION OF THE MEAN acid-base balance of the arterial blood in the triaxial coordinates diagram of Shock and Hastings (7) in sea level residents and in men living permanently at various altitudes (solid circles and square), as compared with the acid-base balance in the party members of the High Altitudes Expedition to Chile (crossed circles), studied during a period of 14 weeks of gradual ascent and residence at high altitudes. The latter values and the one corresponding to the permanent residents at 5340 meters have been taken from the literature (3, 6). Figures give the altitude level, in kilometers, at which the observations were carried out. The observations in the permanent residents (solid circles and square) were made in different groups of subjects living at various altitudes; those corresponding to the temporary residents (crossed circles) were made in only one group of men, observed at various altitudes during the ascent.

Figure 9 shows in the triaxial coordinates diagram of Shock and Hastings the nature of the acid-base displacement in the groups of permanent residents studied by us at various altitudes, as compared with the one corresponding to the party members of the High Altitudes Expedition to Chile.

In this diagram, as well as in the one given in figure 4, we have incorporated the data obtained by the above-mentioned expedition in the study of a group of residents at 5340 meters of altitude (6), data which correlates well with our findings. The study of figure 9 reveals that in the permanent and temporary residents there is a lowering of the  $(\text{BHCO}_3)_s$  and of the  $(\text{pCO}_2)_b$ . However in the first groups the resulting pHs, although within the normal limits of variation, lies to the left of the line corresponding to a value of 7.40, that is, with some deviation to the acid excess, while in the second groups it is placed to the right of that line, in the zone of the  $\text{CO}_2$  deficit or respiratory alkalosis. It is also interesting to note in this diagram that in the native residents there is no tendency to a further lowering of the pHs as the altitude increases; in the case of the temporary residents the relation of the pHs to the level of altitude is not so well defined but, as a whole, the alkaline displacement, evident at moderate altitudes, has a tendency to remain about the same at the highest places.

#### DISCUSSION

Our observations indicate that the influence of a low pressure environment on the properties of the arterial blood cannot be defined in simple terms of relationship to the level of altitude or pressure. The length of the exposure, and its character of temporary or permanent, introduces a fundamental factor of variability. The subject who just arrives to high altitudes presents a different situation to the one found in the man born and raised in this environment. In regard to the oxygen transport the newcomer, studied within the first two hours after arrival, shows a marked decrease in the amount of oxygen carried by the hemoglobin and has practically no increase in the combining capacity for this gas, in contrast to the resident in whom the high level of hemoglobin results in a load of oxygen greater than at sea level, in spite of the reduction in the degree of saturation. In connection with the latter characteristic we have found evidence that the degree of anoxia is more marked in the newcomer, as compared with the resident, especially at altitudes over 3000 meters. This difference is probably present only in the very early period of exposure, because our values for the percentage of  $\text{HbO}_2$  in the native residents are very similar to those found, in previous investigations, in people who have been subjected to a low pressure or have been living at high altitudes for some time.

That the lower saturation, found after arrival, is not due to a difference in the affinity of hemoglobin for oxygen can be inferred from previous investigations (15, 16). A decrease in the permeability of the alveolar membrane during the first few hours of exposure could be the responsible factor; however, it is more likely that the higher degree of arterial oxygen saturation in the native residents is caused by a more efficient pulmonary ventilation. We have observed, at an altitude of 4540 meters, a higher alveolar  $pO_2$  in native residents as compared with a group of men studied within the first two hours after arrival (23).

In the investigations reported in this paper we have found further evidence that in men living at various altitudes the level of polycythemia has a striking inverse relationship to the degree of anoxemia, as it has been previously reported (13).

From our observations and from a comparative study with data found in the literature, it appears that the acid-base balance under the influence of a low pressure environment is also largely regulated by the length of the exposure. Immediately after arrival to high altitudes there are not very significant variations; later on, if the exposure is continued, a condition of alkalosis gradually develops, due to the fact that the reduction in  $(pCO_2)_b$  which takes place is not accompanied by a proportional decrease in the alkaline reserve; consequently, the pHs increases. Finally, in the native resident an equilibrium is reached between these characteristics and although both are considerably lower than at sea level, the pHs has a normal value, or, according to our findings, a slight tendency to be in the low limits of normal variation. We do not know what are the time limits which separate one period from another. However, it appears likely that the process of alkalosis begins to develop soon after arrival, possibly influenced in great part by the initiation of physical activity, which in association with anoxia overstimulates the respiratory center with a resulting hyperventilation and loss of  $CO_2$ , in contrast with the more gradual and slower loss of bicarbonate through the kidneys. From the studies made by the High Altitude expedition to Chile (3, 6), and recently by Houston and Riley (22), it is evident that the period of alkalosis is one of the characteristics of the acclimatization process, with a duration of several weeks and even months. How soon a temporary resident acquires the acid-base condition of the man living permanently at high altitudes is a problem not yet solved.

Our findings in the residents at high altitudes agree with those of Dill, Talbott and Consolazio (6), who in 1937 described the physiochemical properties of the blood in a group of miners living at an altitude of 5340 meters. We have observed in the residents that the decrease in  $(pCO_2)_b$  and in the alkaline reserve are proportional to and have a linear relationship to the



level of altitude up to about 5000 meters, when, and according to the data given by the investigators just mentioned, both reductions become more marked but keeping, as in lower altitudes, a pHs within normal limits. Thus the increased buffer value brought about by the greater volume of cells and the elevated oxyhemoglobin content in the blood of the high-altitude residents is accompanied by a decrease in the alkaline reserve available for combining with fixed acids. In spite of the last disadvantage the native inhabitant at high altitudes is able to tolerate strenuous physical activity. The mechanisms involved in this process are being studied in our laboratories at the present time.

It must be finally emphasized that an exposure of a few weeks and even months to a low-pressure environment approximates, but does not place in a similar physiological pattern, the temporary and the permanent resident at high altitudes. This fact suggests that the study of the latter subject must be the logical source of comparative data to be used in the evaluation of how complete acclimatization is in the newcomer and in the temporary resident.

#### SUMMARY

The gas content, oxygen saturation and the acid-base balance of the arterial blood have been determined in healthy residents at sea level and in Indian natives born and raised at high altitudes and living permanently at various levels on the Andean zone. Similar investigations have been made in different groups of newcomers at high altitudes within the first two hours after arrival. The results obtained have been compared with those reported in previous and related studies.

Our observations show that the properties of the arterial blood under the influence of a low-pressure environment are largely determined by the length of the exposure in addition to the level of pressure. A man just arrived at high altitudes differs from the temporary resident, and the latter, even if his residence is of a few weeks' duration, does not reach the same characteristics observed in the man born and living permanently at high altitudes.

The period of time which corresponds to the evolution of the process of acclimatization, and its merging into a condition of adaptation, is not known at the present time.

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# *Estimation of Critical Dead Space in Respiratory Protective Devices<sup>1</sup>*

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INCREASING EXTERNAL DEAD SPACE is an inevitable accompaniment to the use of various respiratory protective devices. Frequently minimal dead space may not be compatible with other essential features of design, especially in rescue apparatus.

The data to be presented in this paper were gathered in response to the practical need for estimation of maximal external dead space consistent with 'normal' respiratory behavior. Combined with information from other sources they are used as a basis for estimation of a 'critical', or a maximum permissible, value. In addition, the response to mild exercise presents some unanticipated relationships.

## METHOD

A closed circuit, dry, double-tube metabolism apparatus (McKesson 'Metabolor') was employed for recording tidal volume, respiratory frequency, ventilation rate and oxygen consumption. The amount of rebreathing was varied by insertion of rubber tubing, of bore commonly employed in oxygen equipment, between the subject and recording apparatus. Respiratory pressures were measured by a water manometer attached to the mask and are expressed as average maximal pressures over each test period. When desired the Pauling oxygen tensimeter was connected into the system and samples of gas circulated through it by means of a small pump.

All tests were made at ground level pressure. The 7 subjects were adult males, tested 1.5 hours postprandially. Three 8-minute control periods were followed by several test periods with added dead space and, when desired, the control values redetermined. Alveolar samples were collected over mercury after forced expiration at the end of each test period and analyses for oxygen and carbon dioxide carried out on a Shepherd apparatus. Tests were arranged to assure steady state conditions, and data indicating deviations from the steady state were discarded.

Owing to the length of the experiments a comfortable mask was substituted for the conventional mouthpiece. Comparisons were made between the mask alone and

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<sup>1</sup> Part of the material in this paper was contained in a report circulated by the Committee on Aviation Medicine, National Research Council, as Report No. CAM 238, dated January 1, 1944, and in a "Symposium on Military Physiology," Research and Development Board, Digest Series 4 GE 61/1, December 4-6, 1947, pp. 71-77.

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mask plus additional tubing. An additional series was run to compare the effects of the mask (approximately 100 ml.) and the mouthpiece. No significant differences were observed in this latter case, but the experimental comparisons must be considered as from a base line of 100 ml. external dead space.

Exercise, where present, consisted of pedalling a stationary bicycle at a rate and load sufficient to double the rate of oxygen consumption over the sitting-rest value.

Statistical significance of the effects was determined by application of the Fisher 't' test (1) and in one case by calculation of the fiducial limits of the mean.<sup>4</sup>

## RESULTS

Table 1 illustrates the effect of various added dead spaces up to 540 ml. on alveolar  $p\text{CO}_2$ , tidal volume and respiration rate. Changes which are *not* significant statistically are indicated by an asterisk in the table. Except for one value it is seen that alveolar  $p\text{CO}_2$  does not change significantly under resting conditions until an added dead space of 540 ml. is reached; under exercise conditions a significant rise occurs at 320 ml. Significant changes in tidal volume appear almost immediately on adding dead space, while respiration rate shows no change except with the largest volume under exercise conditions. Not shown in the table is the fact that oxygen consumption showed no real change in any case.

Figure 1 presents the alterations in rate of pulmonary ventilation as a function of added external dead space. All increases were found to be significant statistically except the first point in the presence of exercise. Obviously, changes in pulmonary ventilation occur at rest with only small increments in dead space, and, combined with the data contained in table 1, it is clear that this increase is accomplished largely by increasing the tidal volume rather than the respiration rate, a not unexpected response (2).

An unexpected feature of the data in figure 1 is the fact that the initial increases in pulmonary ventilation were considerably smaller in the presence of light exercise than under resting conditions. This was found to be true on both an absolute and on a percentage basis. The limits of the range of expected variation of any given observation from the mean are indicated in the figure (calculated as fiducial limits). The lessened response to small dead spaces under exercise conditions is clearly significant. In contrast to this, increments in dead space beyond 150 ml. added (250 ml. total) dead space result in ventilation increments of the same or slightly greater magnitude than under resting conditions. Thus the regression lines are nearly parallel but displaced by a factor of approximately 2 liters per minute in the magnitude of response to any given dead space.

Table 2 presents the changes in respiratory pressures occurring on addition of dead space. The shape of the space was chosen to simulate

<sup>4</sup> Thanks are due to Dr. M. R. Zelle for this latter calculation.

current oxygen supply equipment practices. While small, these changes are significant statistically in the majority of instances. Changes in resistance to breathing were subjectively the most noticeable element of difference among various tubes. In fact, subjective response followed more closely the pressure patterns than any of the other parameters. Not shown in the tables are readings for a tube with a 250 ml. volume but fitted with a restriction causing about one cm. of water further increase in pressure drop.

TABLE 1. CHANGE IN AVERAGE ALVEOLAR  $pCO_2$ , TIDAL VOLUME AND RESPIRATION RATE ON ADDING VARIOUS EXTERNAL DEAD SPACES

DEAD SPACE ADDED <sup>1</sup>	ALVEOLAR $pCO_2$		TIDAL VOLUME <sup>2</sup>		RESPIRATION RATE	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
ml.	mm. Hg	mm. Hg	ml.	ml.	Resp/min.	
150	2.0 <sup>1</sup>	0.1 <sup>1</sup>	132	6 <sup>1</sup>	-0.3 <sup>1</sup>	-0.3 <sup>1</sup>
250	3.0	2.1 <sup>1</sup>	209	111	0.6 <sup>1</sup>	-0.4 <sup>1</sup>
250 <sup>4</sup>	1.2 <sup>1</sup>		163		1.0 <sup>1</sup>	
320 <sup>4</sup>	0.9 <sup>1</sup>	4.3	144 <sup>1</sup>	114	1.5 <sup>1</sup>	-0.3 <sup>1</sup>
450 <sup>4</sup>	2.2 <sup>1</sup>	4.0	347	310	0.3 <sup>1</sup>	0
540	5.6	4.3	410	386	-0.3 <sup>1</sup>	-1.5

<sup>1</sup> Change not significant statistically (Fisher 't' test,  $p$  value  $> 0.01$ ).

<sup>2</sup> Total dead space 100 ml. greater. <sup>3</sup> STP dry. <sup>4</sup>  $\frac{3}{4}$  in. bore, others  $\frac{1}{2}$  in. bore.

This tube was subjectively less comfortable than any but the 540 ml. volume, in spite of the fact that ventilation rate was considerably higher with the latter tube.

Experiments in which oxygen tension was measured indicated that this was maintained constant in both the mask and alveoli until alveolar  $pCO_2$  began to rise, in which case  $pO_2$  fell in proportion to the rise in  $pCO_2$ . Statistical validity of changes in  $pO_2$  was not tested.

#### DISCUSSION

Physiological effects of added external dead space are related principally to the increased volume for rebreathing and the increased resistance to gas flow. The data presented above corroborate the opinion that, subjectively, the resistance factor will probably outweigh the rebreathing factor as bulk is increased, especially with equipment of current design. The data also indicate that dead space might be increased safely in certain instances to reduce resistance. Complementary to this is the fact that alveolar  $pCO_2$  may be increased by resistance to breathing (3, 4), and thus reducing resistance might automatically compensate to a certain extent for the increase in dead space.

It is clear that increases in pulmonary ventilation prevent a rise in alveolar  $pCO_2$  under resting conditions until fairly large dead spaces are

added. In the presence of light exercise the addition of dead space is not met initially by as large increases in ventilation as at rest, possibly because of the smaller ratio of the added dead space to the tidal volume or to changes in physiological dead space accompanying the increased tidal volume (2). It will be noted, however, that significant rises in alveolar  $p\text{CO}_2$  occur at smaller added dead spaces under exercise than under sitting-rest conditions. Hence the physiological adjustment may be considered as less adequate for maintenance of normal gas tensions under conditions of light exercise.

Studies complementary to the present one have appeared in the Italian literature (5, 6). Tomasso (5) exercised his subjects lightly at ground level prior to testing, while Margaria (6) determined the effect of added external dead space on altitude tolerance. Thus the conditions of these studies are not strictly comparable to the present one. These investigators

TABLE 2. EFFECT OF ADDED EXTERNAL DEAD SPACE ON RESPIRATORY PRESSURES

DEAD SPACE ADDED <sup>1</sup>	BORE	INCREASE IN MAXIMAL INSPIRATORY PRESSURES <sup>2</sup>		INCREASE IN MAXIMAL EXPIRATORY PRESSURES <sup>2</sup>	
		Rest	Exercise	Rest	Exercise
ml.	in.	cm. water	cm. water	cm. water	cm. water
150	$\frac{5}{8}$	0.4 <sup>1</sup>	1.8	0.7 <sup>1</sup>	0.9 <sup>1</sup>
250	$\frac{3}{4}$	1.2	1.9	1.1 <sup>1</sup>	2.2
250	$\frac{3}{4}$	1.4		0.5	
320	$\frac{3}{4}$	1.1 <sup>1</sup>	1.4	0.8 <sup>1</sup>	1.2
450	$\frac{3}{4}$	1.0	2.4	1.6	1.9
540	$\frac{5}{8}$	3.3	5.3	4.8	3.8

<sup>1</sup> Change not significant statistically (Fisher 't' test,  $p$  value  $> 0.01$ ).

<sup>2</sup> Total dead space 100 ml. greater.      <sup>3</sup> Average maximal pressures.

did not test the statistical validity of their results, but it is clear in both instances that alveolar  $p\text{CO}_2$  remains constant up to added dead spaces approximating 300 to 350 ml. Margaria's results show that at altitude (7000 meters) alveolar  $p\text{O}_2$  is influenced by dead space only when ventilation is insufficient to prevent a rise in alveolar  $p\text{CO}_2$ .

Data on pulmonary ventilation and alveolar  $p\text{CO}_2$  at dead spaces between 40 and 1575 ml. have been obtained by Otis *et al.* (7) and Fenn *et al.* (8) for other purposes. Their results indicate a rapid rise of pulmonary ventilation and alveolar  $p\text{CO}_2$  at dead spaces higher than those employed in the present study (15.2 l/min. with 785 ml. increment in dead space, and 26.4 l/min. with 1535 ml. increment). Alveolar  $p\text{CO}_2$  values for subjects breathing air at 16,000 feet (8) show that hypocapnia may, under these conditions, decrease the effect of the smaller dead spaces on ventilation and alveolar  $p\text{CO}_2$  at least until equilibrium conditions can be established.

The effect on pulmonary ventilation of the dead space contained in the A-13 and A-14 oxygen masks and of various lengths of tubing added thereto was determined by Hall, Wilson and Dahling (9) under conditions of rest and light exercise. Their report appeared in the military literature just prior to our preliminary report. A smaller response of the ventilation rate under conditions of light exercise compared with rest is apparent in their data where they are expressed as per cent change. It is not as clear as in figure 1 above when considered on the basis of absolute values (9,

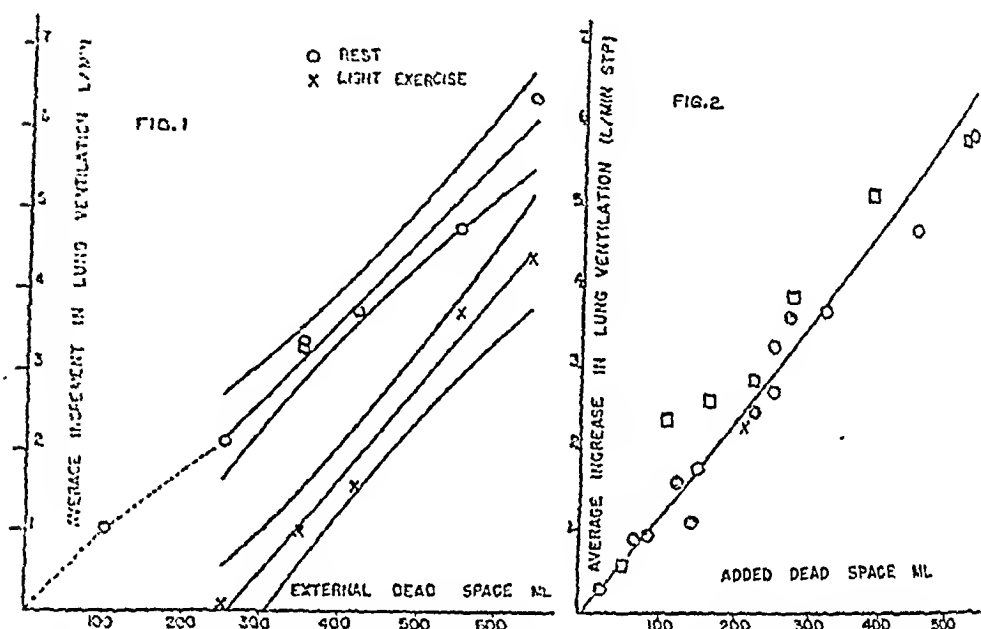


Fig. 1. EFFECT OF EXTERNAL DEAD SPACE on pulmonary ventilation under conditions of rest and light exercise. Regression lines were fitted by the method of least squares and the fiducial limits indicated for each set of points (excluding the value at 100 ml. under resting conditions, since no comparable point existed under exercise conditions). The linearity of the exercise response as zero dead space is approached is probably spurious, but it is the best representation of available data. Rates are expressed at STP dry.

Fig. 2. COMPOSITE PLOT of effect of added dead space on average pulmonary ventilation rate under resting conditions. Symbols:  $\circ$  = present data;  $\square$  = Tomasso, (5);  $\bullet$  = Hall *et al.* (9);  $\times$  = Otis *et al.* (7). Since the initial dead space was not identical in each series, nor was the figure given in every case, the abscissa represents added dead space rather than total as in figure 1. Tomasso's subjects exercised lightly before the test but were at rest during the determinations.

table 1). This may be attributed in part to the relatively short range of dead spaces added, but other variables may have contributed.

Since the response of the pulmonary ventilation rate is apparently the most sensitive indication of physiological adjustment, and also, in many instances, an important consideration in equipment design (especially in determining oxygen economy in open circuit systems) the data from the several sources mentioned above are summarized in figure 2. The response appears to be linear up to at least 500 ml. added dead space. With larger

volumes the ventilation may not respond linearly, although the data are rather meagre in this range.

Estimation of a 'critical,' or a maximum permissible dead space is governed by the criterion chosen. No volume tested above 100 ml. could be considered without effect on pulmonary ventilation as seen in both the present and other studies. This is of practical importance particularly in devices operating on the demand principle. If maintenance of constant and nearly normal alveolar  $\text{CO}_2$  and  $\text{O}_2$  tensions is considered of greatest importance (in contrast to more strictly engineering or comfort factors), the critical *total* volumes would approximate 400 ml. under exercise conditions and 600 ml. under resting conditions. These values may be utilized as a working hypothesis but the increased respiratory effort necessary with volumes of this magnitude may involve fatigue factors of importance in designing apparatus for long periods of use.

#### SUMMARY

1. Effects of added external dead space at sea level pressure have been determined on tidal volume, respiration rate, pulmonary ventilation rate, alveolar  $\text{pCO}_2$ , oxygen consumption and inspiratory and expiratory pressures. Total dead space volumes ranged from 100 ml. to 640 ml., with increments varying from 150 to 540 ml.

2. Pulmonary ventilation and tidal volume were found to be the most sensitive functions by objective measurement, while changes in respiratory pressures were the most sensitive subjectively.

3. Ventilation rate responded less adequately to increase in dead space when the subject engaged in light exercise than under sitting-rest conditions. The increases were smaller on both an absolute and relative basis, and as a result, alveolar  $\text{pCO}_2$  rose at lower dead spaces under exercise conditions.

4. Changes in respiration rate and oxygen consumption rate were negligible under the conditions of the study.

5. 'Critical' dead space depends upon the criterion chosen. All additions above 100 ml. had some effect, especially on pulmonary ventilation (and, thus, on cylinder oxygen consumption). If maintenance of alveolar  $\text{pCO}_2$  is chosen as the criterion of safety, critical spaces may be estimated as approximately 600 ml. at rest and 400 ml. under light exercise conditions.

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# *Changes in Response to Inhalation of CO<sub>2</sub> Before and After 24 Hours of Hyperventilation in Man<sup>1</sup>*

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IN STUDIES ON THE EFFECTS of prolonged periods of hyperventilation in human subjects, it was observed that after 24 hours of hyperventilation in a body respirator subjects not only failed to show apnea, but spontaneously overventilated for several hours. This reaction is comparable to the phenomenon of continued overventilation following descent to sea level in persons who have become acclimatized to high altitude (1). On the basis of calculations utilizing the equations derived as part of his multiple factor theory of respiratory regulation (2), Gray has suggested that this continued increased ventilation is due to a change in sensitivity of the respiratory center to arterial pCO<sub>2</sub> (3). In an attempt to help elucidate this question, respiratory ventilation responses to 2.5 per cent, 5 per cent and 7.5 per cent CO<sub>2</sub> in oxygen were determined before and after 24 hours of hyperventilation.

## EXPERIMENTAL PROCEDURE

Three young, healthy, male medical students were ventilated at a rate approximately two to three times normal for 24 hours in a body respirator.<sup>2</sup> Two days prior to the day of hyperventilation, subjects were placed on a diet consisting of University of Minnesota Hospitals diet II (4), milk and water *ad libitum*. This diet was maintained until 24 hours after completion of the hyperventilation period. On each of the two days prior to the experimental period the subject came to the laboratory for ventilation studies. After the subject had rested in the supine position for 30 minutes, respiratory minute volume and respiratory rate were determined with the subject breathing 100 per cent oxygen, 2.5 per cent CO<sub>2</sub> in oxygen, 5 per cent CO<sub>2</sub> in oxygen and 7.5 per cent CO<sub>2</sub> in oxygen, in that order. Resting ventilation and CO<sub>2</sub> response determinations were repeated one hour after the 24 hours of hyperventilation, and at daily intervals for several days, or until the response had returned to the control level. Minute volumes were measured

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<sup>2</sup> The respirator employed was the commercial model of the J. H. Emerson Company, to whom we are indebted for its loan.

by the open circuit method using a modified, tightly fitting A-15 Army aviation mask and collecting the exhaled air in a 100-liter balanced spirometer. Subjects noticed no resistance to breathing with this system except at very high rates of flow, i.e. 60 to 80 liters per minute. Normal resting minute volumes were measured by allowing the subject to breathe 100 per cent oxygen from a 5-liter rubber bag which was continuously filled from a cylinder of compressed oxygen. It has recently been shown that changing normal human subjects from air to 100 per cent oxygen at sea level has little or no effect on ventilation rate (5). Ventilation response to  $\text{CO}_2$  was determined using the same apparatus and filling the bag from a cylinder containing the proper mixture of  $\text{CO}_2$  and oxygen.

Blood samples were drawn from either the brachial or femoral artery before each series of ventilation determinations. Precautions were observed to prevent exposure of the blood to air, and .01 ml. of sodium heparin solution per ml. of blood to be drawn was used as an anticoagulant. No correction has been made in the data for this dilution. Immediately after drawing the blood, one ml. was introduced anaerobically into a specially constructed glass electrode pH meter maintained at  $38^\circ \text{C}$ . and the pH was determined. This instrument uses the circuit described by Burr *et al* (6). Plasma from 10 ml. of blood was separated by centrifugation under oil which had been previously equilibrated with a mixture of gas containing  $\text{CO}_2$  at a tension of 40 mm. Hg at  $38^\circ \text{C}$ ., and the plasma  $\text{CO}_2$  content was determined with the Van Slyke manometric apparatus.

Carbon dioxide capacity ( $T_{40}$ ) was similarly determined on plasma separated from blood which had been equilibrated for 30 minutes at  $38^\circ \text{C}$ . with a gas mixture containing  $\text{CO}_2$  at a pressure of 40 mm. Hg and oxygen at a pressure of approximately 150 mm. Hg.

## RESULTS

Respiratory minute volumes, blood pH, plasma  $\text{CO}_2$  content and  $\text{CO}_2$  capacity as determined before, during and after 24 hours of hyperventilation are presented in table 1. Arterial plasma  $\text{CO}_2$  content decreased an average of 8.9 vols. per cent in one hour of hyperventilation and an average maximum of 18 vols. per cent during the 24-hour period. This represents a reduction of 14.2 per cent and 29 per cent of the average control values, respectively. With this fall in  $\text{CO}_2$  content, arterial pH increased an average of 0.10 pH units in one hour, 0.16 pH units in 12 hours, and 0.12 pH units in 24 hours as compared with the average control arterial blood pH.

Plasma  $\text{CO}_2$  capacity showed no consistent change in the first hour of hyperventilation, then fell steadily until sometime between one hour and 24 hours after artificial hyperventilation was discontinued. The lowest value recorded at one hour after hyperventilation, averaged 8.8 per cent below

the pre-hyperventilation level. Twenty-four hours later  $\text{CO}_2$  capacity had increased, but was still 6.7 per cent below the control average.

It should be pointed out that the minute volumes measured with the subject in the respirator were sample values and not continuous measurements of ventilation over the 24-hour period. The ventilation volume depends upon several factors in addition to the pressure gradients set up by the respirator.<sup>3</sup> *Subject W. F.* exhibited marked signs of tetany when, in the initial setting of the respirator pressure gradient, his ventilation ratio

TABLE 1. RESPIRATORY MINUTE VOLUME AND PLASMA  $\text{CO}_2$  CONTENT, pH, AND  $\text{CO}_2$  CAPACITY ( $T_{40}$ ) BEFORE, DURING AND AFTER 24 HOURS OF HYPERVENTILATION

SUBJECT	H. B.				W. F.				C. B.			
	Min- ute Vol.	Plasma			Min- ute Vol.	Plasma			Min- ute Vol.	Plasma		
		$\text{CO}_2$	pH	$T_{40}$		$\text{CO}_2$	pH	$T_{40}$		$\text{CO}_2$	pH	$T_{40}$
	l.	vol. %		vol. %	l.	vol. %		vol. %	l.	vol. %		vol. %
Before hypervent...	6.9	59.9	7.40	59.8	7.7	64.4	7.36	64.5	7.8	59.2	7.36	62.7
1 hr. hypervent....	14.3	50.8	7.51	63.3	12.3	56.5	7.42	60.4	26.5	49.7	7.50	64.0
12 hr. hypervent...	19.5	48.7	7.52	62.9	12.7	40.5	7.56	61.1	25.0	48.7	7.52	59.0
24 hr. hypervent....	18.7	44.0	7.50	57.2	17.0	45.0	7.47	59.6	21.1	44.9	7.52	59.0
1 hr. after hypervent.....	10.2	50.5	7.42	56.4	6.7	53.4	7.37	57.9	9.1	50.6	7.36	56.2
24 hr. after hypervent.....	7.1	50.1	7.36	56.8	6.9	58.3	7.37	60.0	7.0	51.2	7.40	57.6

exceeded 2 for any length of time. As a result he probably was overventilated less than the other 2 subjects. *Subject H. B.* was uncomfortable in the respirator and slept little or none during the 24 hours.

Table 2 gives normal resting ventilation and ventilation response to the three mixtures of  $\text{CO}_2$  in oxygen before and after 24 hours of hyperventilation. Ventilation ratio is expressed as the ratio of minute volume to the resting minute volume breathing oxygen before hyperventilation. The response of *subjects H. B.* and *C. B.* before hyperventilation fall within the normal range as reported by Peabody (7), but after 24 hours of overventilation the responses of these 2 subjects were markedly elevated. The control response of *W. F.* is somewhat below Peabody's range of normals and following the stay in the respirator he showed an increased response only on the highest concentration of  $\text{CO}_2$  used. This increase in response, however, continued for 72 hours.

<sup>3</sup> It was observed, for example, that *subject C. B.*'s respiratory minute volume fell markedly during sleep. Attention was called to this phenomenon by the occurrence of laryngeal stridor when this subject fell asleep. By using a mask that allowed the subject to sleep while ventilation records were being made, it was demonstrated that while asleep he was being ventilated very little in excess of his normal resting rate, regardless of the pressure differential being imposed by the respirator. The mechanism of this closure of the airway is entirely unknown. It became necessary to keep *subject C. B.* awake during the remaining 18 hours of the time in the respirator in order to insure that he was being hyperventilated.

C. B. an increased normal resting ventilation was evident after the arterial pH had returned to its control value.

It is interesting to note the wide variation in effects of 24 hours of hyperventilation on CO<sub>2</sub> responses among the 3 subjects. W. F. showed only a small change in response, H. B. exhibited a marked increase in response which was still evident after 11 days and C. B. gave a moderate response falling between these two extremes. Some of this apparent variation among individuals however may be due to differences in the degree of over-ventilation imposed during the 24-hour experimental period.

The fact that this increased ventilation does continue following as short a period of hyperventilation as 24 hours should be of some significance to the clinician in the handling of patients in a respirator. It has been observed (8) that poliomyelitis patients in respirators are often ventilated at a rate in excess of normal, according to physiological standards. It has also been noted that some of these patients who have been overventilated, when released from the respirator, maintain this elevated ventilation rate until fatigue occurs. These clinical observations are in line with the findings of this study and serve to emphasize the principle that, in order to avoid additional respiratory embarrassment to the partially paralyzed patient when attempts are made to free the patient from the respirator, ventilation should not be maintained over long periods of time at a rate in excess of that necessary to maintain normal pCO<sub>2</sub> and normal oxygen tension.

#### SUMMARY

Respiratory ventilation responses to CO<sub>2</sub>-oxygen mixtures before and after 24 hours of hyperventilation in a body respirator were determined on 3 young, healthy, male medical students. Two of the subjects showed an increase in ventilation response to the three concentrations of CO<sub>2</sub> after the hyperventilation, while the third exhibited an increase in response to the highest concentration of CO<sub>2</sub> but not to the two lower concentrations. Stimulus response curves, constructed by plotting alveolar pCO<sub>2</sub> against alveolar ventilation ratio, showed an increase in slope in 2 of the 3 subjects when responses before and after 24 hours of hyperventilation are compared.

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## *Studies on Aerosols V. Effect of Dust and Pneumodilating Aerosols on Lung Volume and Type of Respiration in Man*

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IN PRELIMINARY UNPUBLISHED EXPERIMENTS (1943) it was shown by Philippot and one of us that inhalation of carbon dust caused an immediate and marked reduction in lung volume in man. In 1945, Filley, Hawley and Wright (1), using Sollmann and von Oettingen's technique (2) of the isolated and perfused lung, confirmed the results of Gardner and Dworski (3) and of Hawley (4) and have shown that colloidal silica produced bronchial spasm with obstruction. On silicotic patients, Wright (5) has also obtained a measurable increase in the maximum breathing capacity following subcutaneous injection of 0.5 cc. of 1:1000 epinephrine, suggesting that bronchial spasm is responsible for a part of their respiratory disability.

In the present work, tests were carried out on three healthy human subjects to determine the effect of inhaled dust on respiration. The following dusts were used in these studies: powdered aluminum (McIntyre), aluminum hydrate (H-1010 Aluminum Co. of America), willemite, dolomite, calcschist, copper sulfide and zinc sulfide. The first two are processed materials, while the last five are naturally occurring substances obtained from mined ores.

The mean size of the inhaled dust particles was less than one micron and the quantity inhaled did not cause any subjective sensation. Our purpose was to determine: a) the effect of single and repeated inhalations of dust on pulmonary volume and type of respiration; b) the effect of pneumodilating aerosols on the pulmonary volume after inhalation of dusts; c) the effect of dust upon pulmonary volume after pneumodilation by such aerosols.

## METHODS

The lungs of the subject were made a part of a closed circuit (6) consisting of a Model 185 McKesson 'Metabolor' connected with various flasks as shown in figure 1. Essentially, this apparatus is comprised of: a kymograph; a low resistance rubber bellows which is the only part of the circuit, other than the subjects' lungs, which can change in volume; various devices for introducing dusts and aerosols into the circuit without changing its volume; an oxygen supply to continuously replace metabolized oxygen; and a soda-lime trap to absorb exhaled carbon dioxide. The kymograph record is an ink tracing on calibrated paper which is fed through the machine by a constant speed motor. The ordinates of the graph are calibrated in liters and deciliters and the abscissas in minutes and tenths of a minute. The machine is designed so that an upward shifting of the tracing represents increased lung volume (less air in the bellows), while a downward shifting shows constriction of the lung. From the tracing the frequency and depth of individual respiration as well as changes in lung volume are easily determined.

As may be seen in figure 1, three flasks, each of 12 liters capacity, are connected to the circuit. A three-way valve permits rapid transfer of the air current from one flask to another as desired, but at no time is more than one flask included in the circuit. The total volume of the circuit is thus maintained constant at all times.

The dust administered was suspended in air by a simple device shown in figure 1. Fifty mg. of the dry material, previously passed through a 200-mesh sieve, was placed in the dust-generating tube (fig. 1). With the dust flask cut off from the rest of the circuit and open to the air, the dust was dispersed by the sudden release of about 200 ml. of compressed air. A few seconds were allowed for the pressure in the flask to return to equilibrium, after which the outlet tube was closed. By means of the three-way valve the dust flask could then be substituted for the normal air flask in the circuit.

The quantity of dust reaching the mouthpiece was determined by collection on a weighed filter paper (Whatman no. 50). Twelve liters of dust-laden air were drawn through the filter paper at a rate of six l./min. by means of a small air pump. To determine approximate mean size of the dust particles reaching the mouthpiece, the air in the dust flask was forced by water displacement (six l./min.) into a similar flask attached to the mouthpiece. A vaseline-coated slide was placed in the latter flask prior to the introduction of the dust. An overnight period was then allowed for the dust to settle on the slide. The dust particles were measured at a magnification of 1125  $\times$  with the aid of a filar micrometer.





The procedure followed in a typical experiment may be outlined step-wise as follows:

1. Pre-exposure period (2-5 minutes) to acclimate the subject and permit regulation of the oxygen supply to the exact requirements of the subject. When equilibrium had been reached, as evidenced by a uniform tracing along a horizontal line, the following successive exposures were made. Two minutes were allowed for each step and the operator used this time to prepare the desired atmosphere for the next exposure.
2. Dust.
3. Normal air.
4. Aerosol.
5. Normal air.
6. Dust.
7. Normal air.
8. Aerosol.
9. Normal air.
10. Dust., etc.

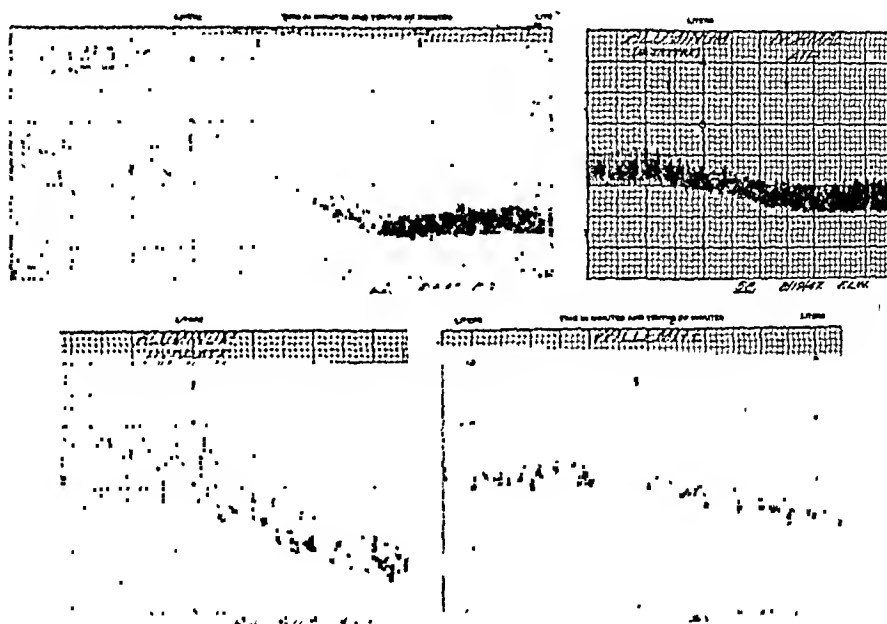


Fig. 2. EFFECT OF INHALATION of fine dust (aluminum powder, aluminum hydrate, willemite) upon the pulmonary volume and type of respiration.

Such a procedure or any desired variation thereof was continued as long as seemed desirable.

## RESULTS

1. *Effect of Dust on Pulmonary Volume (42 Concordant Experiments).* All of the dusts studied produced pneumoconstriction when inhaled (figs. 2-8). The reduction in pulmonary volume occurred promptly and there were no detectable differences between the effect of a siliceous material such as willemite (zinc silicate) and the supposedly therapeutic dusts such as metallic aluminum (8, 9) or aluminum hydrate (10). Since the decrease in pulmonary volume often exceeded one liter, it appears reasonably certain that the smaller respiratory passages contracted since constriction of the bronchi alone could hardly produce such a large change. It may also be

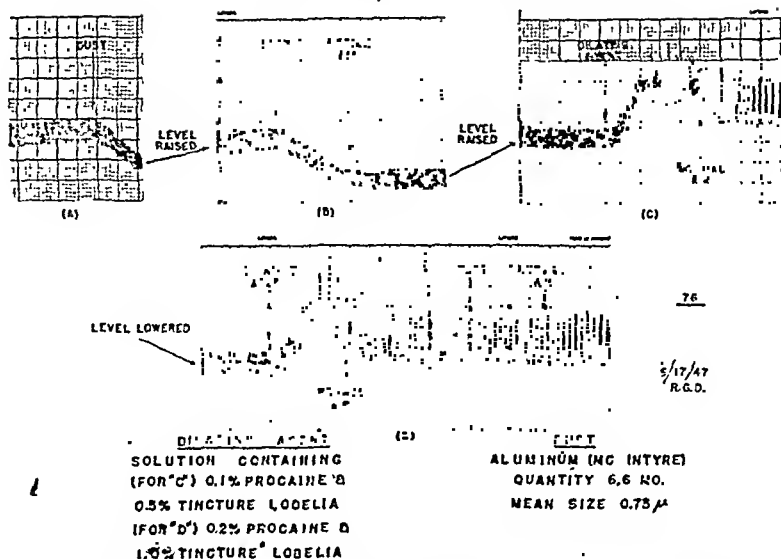


Fig. 3. EFFECT OF ALUMINUM POWDER upon the pulmonary volume before and after dilation of the lungs by a pneumodilating aerosol.

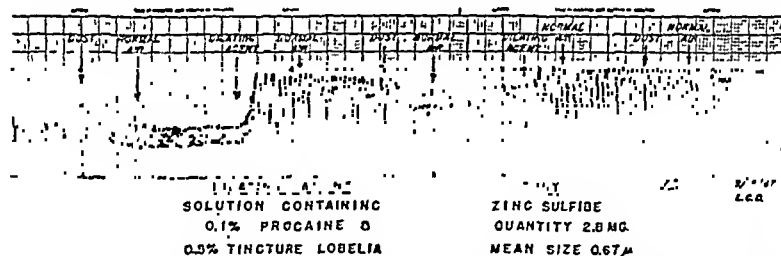


Fig. 4. EFFECT OF ZINC SULFIDE DUST upon the pulmonary volume before and after dilation of the lungs by a pneumodilating aerosol.

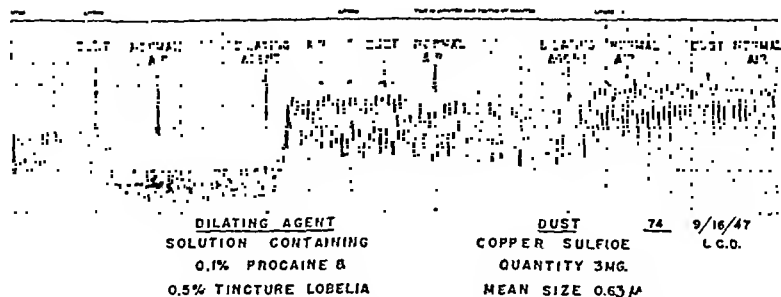


Fig. 5. EFFECT OF COPPER SULFIDE DUST upon the pulmonary volume before and after dilation of the lungs by a pneumodilating aerosol.

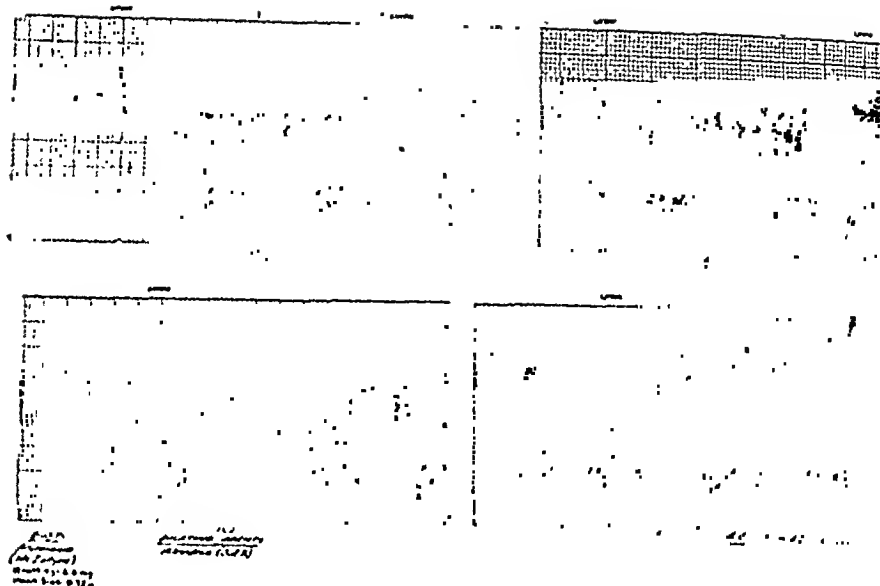


Fig. 6. PROGRESSIVE REDUCTION of pneumoconstricting power of aluminum dust by repeated administrations of pneumodilating aerosols.

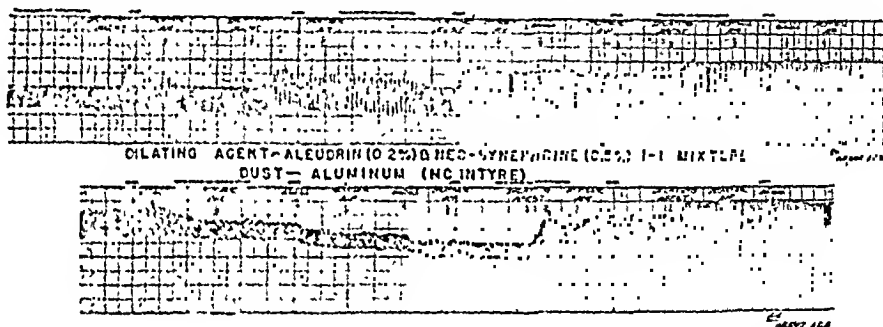


Fig. 7. *Lower tracing.* EFFECT OF REPEATED ADMINISTRATIONS of aluminum dust upon the pulmonary volume and type of respiration. Dilation of the lungs prevents further constriction by dust. *Upper tracing.* Prevention of dust-constricting action by dilating aerosols.

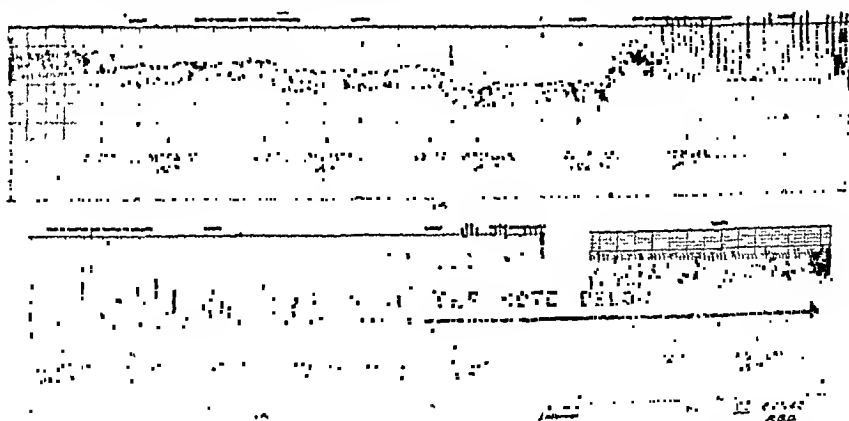


Fig. 8. *Upper tracing.* EFFECT OF REPEATED ADMINISTRATIONS of aluminum dust upon the pulmonary volume and type of respiration. *Lower tracing.* Dilation of the lungs prevents further pneumoconstriction by dust. NOTE: Owing to a momentary accidental leakage in the system, the indicated increase in lung volume is recorded approximately 500 ml. greater than it should be.

seen from figures 2 to 8 that as the lung contracted, a rapid shallow respiration appeared which persisted for at least several minutes after the subject was returned to the normal air circuit. It is to be noted that in most of the cases, the fall of the respiratory tracing is abrupt, which indicates that it is not likely to be produced by a modification in the oxygen intake. On the other hand, on account of the severe tachypnea rapidly induced by the inhalation of dust, one should expect an increase in the metabolic rate to take place. This, of course, with the technique used (based upon a constant rate of oxygen flow) should raise the tracing. It is therefore probable that the recorded constriction, as evidenced by the lowering of the tracing, is actually greater than that shown.

2. *Effects of Repeated Administrations of Dust (10 Concordant Experiments).* A number of experiments were made in which the subject inhaled dust more than once with only a short interval between doses, during which time normal air was breathed. The second administration of dust resulted in accentuation of the symptoms described above. Pneumoconstriction was more pronounced and respiration was more frequent. A third dose of dust intensified these effects to a still greater degree. This is shown clearly in the first part of figures 3 and 8 and in the second tracing in figure 7. For example, three successive administrations of aluminum powder produced a constriction of more than one liter, while at the same time the respiration quadrupled in frequency.

3. *Effect of Pneumodilating Aerosols upon Pulmonary Volume after Pneumoconstriction by Dust (33 Concordant Experiments).* As a source of pneumodilating aerosols, the following aqueous solutions were employed: Aleudrin (0.2 per cent), a mixture containing aleudrin (0.1 per cent) and neosynephrine (0.25 per cent), and a mixture containing procaine and tincture of lobelia in concentrations ranging from 0.1 to 0.2 per cent for procaine and from 0.5 to 1.0 per cent for tincture of lobelia. It has been found in previous work (11) that a mixture of 0.1 per cent aleudrin and 0.25 per cent neosynephrine is a more active pneumodilator than either 0.2 per cent aleudrine or 0.5 per cent neosynephrine alone. The procaine-lobelia mixture exerts a powerful dilating effect and produces no detectable systemic effects.

Administration of an aerosol of any of the above solutions to a subject after his lungs had been constricted by inhalation of a small quantity of dust resulted in a rapid increase in lung volume as indicated on the kymograph tracing. The extent of dilation was such that the lung volume usually exceeded the normal, and as dilation took place, the respiration became slow and deep. After the subject was again placed in the normal air circuit, the lung volume returned slowly to normal, but in no case was there a return

to a constricted state during the period of observation and respiration continued to be slow and deep. These phenomena are shown in figures 3 to 8.

4. *Effect of Dust upon Pulmonary Volume after Pneumodilation by Aerosols (31 Concordant Experiments).* The fact that pneumodilating aerosols can offset the constricting effects of dusts was also shown in a reverse manner. After dilation of the subjects lungs, the same quantity of dust was administered as before. It may be seen that under these conditions the constricting action of the dust is either diminished (figs. 4-6) or entirely absent (figs. 7 and 8). In those cases where some constricting effect was produced by dust after inhalation of aerosol, a second or a third administration of aerosol prevented any pneumoconstriction during subsequent inhalation of dust (figs. 4-6). It is noteworthy that when aerosols are given first, later inhalation of dust does not induce the rapid shallow respiration noted previously. It also appears that if care is taken to dilate the lungs thoroughly shortly before inhalation of dust they do not contract, and the respiration does not change when the subject is exposed to dust (fig. 7).

#### DISCUSSION

Under the experimental conditions described, these experiments have demonstrated several significant facts as follows: a) Inhalation of small quantities of fine dust (mean size  $0.68 \mu$ ) produced no subjective irritation on three normal subjects but induced a rapid shallow type of respiration and a marked reduction in pulmonary volume. The magnitude of the volume change suggests that not only the bronchi but also the alveolar ducts are involved in the constriction. This condition did not disappear immediately when the subjects returned to normal air. b) After a decrease in lung volume induced by inhalation of dust, a few inspirations of aqueous aerosols of active pneumodilating drugs brought the lung volume back to, or above, normal. Simultaneously, the respiration became slow and deep. Upon again inhaling normal air, the subject's respiration and lung volume slowly returned to normal, but in no case observed was there a return to the constricted state. c) Immediately after a pneumodilation of the lungs by aerosols, inhalation of dusts caused little or no pneumoconstriction. After two or three successive dilations, there was no constriction when the subject inhaled the quantity of dust used in these experiments. These findings coupled with other known facts, lead to several interesting conclusions, some of which must necessarily be considered as hypothetical in the absence of clinical proof.

In the first place, it has been shown that inhalation of small amounts of fine dust causes respiratory distress, and it can be assumed that such distress would be accentuated by more severe exposures. This assumption

is borne out in observations by Dr. J. W. G. Hannon, who reported (personal communication) that the initial effect of the inhalation of aluminum powder by silicotic patients is often characterized by symptoms of asthma-like distress even on subjects who subsequently appear to be improved by aluminum therapy. The quantity of dust inhaled in such cases is sufficient to cause blackening of the patient's mouth and tongue, which was not the case in our experiments.

Without arguing the efficacy of aluminum or aluminum hydrate powders as prophylactic or therapeutic agents for silicosis, it may be reasonably inferred that maximum benefit can be obtained only when the aluminum is uniformly distributed throughout the lung.<sup>1</sup> Such distribution appears unlikely when the subject's respiration is shallow. However, the workman who has been given aluminum therapy while in a state of rest or slight activity will necessarily breathe more deeply when engaged in vigorous exercise. There is, therefore, a strong probability that silica dust will be carried to pulmonary depths not reached by the aluminum or aluminum hydrate powder.

Our findings indicate that such unequal distribution could be prevented if the lungs of the workman were dilated with a dilating aerosol prior to inhalation of the aluminum powder. Such a procedure would not only permit penetration of the aluminum to the pulmonary depths but would also alleviate any unpleasantness associated with the aluminum therapy. Ample proof is available that frequent exposures to pneumodilating aerosols such as epinephrine, ephedrine, benzedrine, ethyl-nor-epinephrine, neosynephrin, aleudrine, procaine and aminophylline not only increase the breathing and the general muscular capacity but also produce no harmful systemic effects, provided the exposures are made under conditions which are controlled as to concentration of drug and time of exposure (12-25).

It has been reported by Haldane, Meakins and Priestley (26) that rapid shallow respiration leads to the development of hypoxemia, and conversely that hypoxemia leads to rapid and shallow respiration thus creating a vicious cycle. Since it has been shown that inhalation of fine dust immediately causes the respiration to become rapid and shallow, it can be assumed that prolonged exposures to dust will tend to promote hypoxemia and the vicious cycle described above. The severity and duration of this condition will of course vary with the degree and type of exposure and also with the individual but should not be ignored. Observations by Wright (5) on silicotic subjects are related to this problem. He has found that 'wheeze' is observed more

<sup>1</sup> "To be effective, a large quantity of the inhibitor must reach the same location and probably the same phagocytic cells that contains the quartz particles." (Gardner, L. U. *The Pneumoconioses*. The Medical Clinics of North America, July 1942.)

often in men working underground than on the surface and that these men speak of losing their 'whceze' several months after they return to the surface. Our results indicate that pneumodilating aerosols might be profitably administered to such subjects at the close of the working day, in order to relieve any respiratory distress that might persist after leaving a dusty atmosphere.

The duration of the protection against respiratory disfunction afforded by pneumodilating aerosols has not been determined under working conditions. Thus the degree of protection during the work period is unknown.

#### SUMMARY

It has been shown on 3 human subjects that inhalation of all dusts studied (mean size 0.7 micron) produces a reduction in lung volume and a rapid, shallow type of respiration which continue for some time after the subject has been returned to normal air. In some cases, this results in severe dyspnea. The net effect is a state of incomplete pulmonary expansion which, in the case of silicotic patients, already plays an important rôle in respiratory disfunction. Pneumodilation with aerosols of aleudrin or other active dilators prevents this condition. It has also been shown that the pneumoconstriction caused by inhalation of fine dusts is promptly relieved by the administration of powerful pneumodilating aerosols.

It is, therefore, suggested that subjects prophylactically or therapeutically submitted to aluminum powders be treated with pneumodilating aerosols prior to aluminum inhalation. It is believed that such treatment may enhance the effects, if any, from aluminum therapy.

It is also suggested that field or plant studies be initiated to investigate the potential benefits of pneumodilating aerosol therapy on workmen who have been exposed to dusty atmospheres. Such exposures should be made at the end of the working day under competent supervision, and under conditions which are controlled as to concentration of drug and time of exposure.

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# *Elimination of Carbon Monoxide from the Blood of Acutely Poisoned Dogs<sup>1</sup>*

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IN THE TREATMENT of acute carbon monoxide poisoning the chief objective is the restoration of an adequate oxygen supply to the heart and the brain. Since carbon monoxide exerts its noxious effect by usurping the place of oxygen in the hemoglobin molecule of the erythrocyte, it is obvious that the rate of dissociation of carbonyl-hemoglobin and the concomitant elimination of carbon monoxide gas will affect the rapidity of oxygen restoration. The object of this study was to determine the rate of clearance of carbon monoxide from the blood of dogs which were given resuscitation treatment of several types after exposure to air containing 0.3 per cent carbon monoxide until acute respiratory distress (air hunger or gasping) appeared.

## EXPERIMENTAL

The dogs with which this work was done have been reported on previously (1) in studies on the efficacy of various methods of resuscitation in carbon monoxide poisoning. Since detailed descriptions of the apparatus used in asphyxiation and in resuscitation are given in the previous report, only a brief statement of our methods is necessary.

The dogs were exposed in a closed chamber through which air containing 0.3 per cent carbon monoxide was flowing at a constant rate. At the first sign of air hunger the dogs were removed and the treatment was begun. At the same time blood was drawn from a foreleg vein as soon as possible and at intervals thereafter. The resuscitation procedure was continued until 'normal' respiration was resumed, or until it was obvious that further treatment was useless due to the certain death of the animal. It was im-

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possible to keep the resuscitator mask on the dogs after they became conscious. *Our clearance studies are therefore based on the effect of a few minutes—usually two to four—of treatment followed by a period of four hours during which the animal was allowed to inhale air.*

The following methods of resuscitation were used: I. manual artificial respiration with inhalation of air; II. mechanical artificial respiration with a device of the 'suck and blow' type,<sup>3</sup> using 100 per cent oxygen;<sup>4</sup> III. the same device using 7 per cent carbogen (7 per cent carbon dioxide and 93 per cent oxygen); and IV. mechanical artificial respiration with a positive pressure device,<sup>5</sup> which permits rebreathing, using 7 per cent carbogen. Two control groups were included: in one the dogs were allowed to die in the chamber; in the other, no treatment was given other than removal from the gassing chamber.

For the determination of carbon monoxide about 1.5 cc. of blood were drawn into a syringe containing enough saturated potassium oxalate solution to moisten the inner surface. It was transferred at once to small test tubes which were stoppered with paraffined corks and inverted several times to insure uniform distribution of the oxalate. Blood for the determination of hemoglobin was drawn previous to exposure into a syringe containing a few crystals of potassium oxalate and likewise transferred to the small tubes.

In addition, determination of carbon monoxide content was made on the blood of dogs which did not survive. Samples were also taken from the right auricle, left ventricle, portal vein and hepatic vein. Determinations were also made on the macerated liver and spleen of a few animals.

Photoelectric spectrophotometric measurements were made on the specimens as quickly as possible (within 3 hours) in order to avoid possible degradation of the blood pigments. Each specimen was treated as follows: One cc. of the oxalated blood, accurately measured, was diluted to 250 cc. with 0.2 per cent aqueous ammonia solution. The diluted blood was mixed and a 50-cc. portion was centrifuged for 15 minutes at about 1750 r.p.m. This procedure removed a small amount of extraneous material and yielded optically clear solutions.

A portion of each clarified solution was used to rinse a well cleansed glass or quartz spectrophotometer solution cell and finally the filled cell was placed in the Beckman Quartz Spectrophotometer for comparison with an optically matched cell filled with distilled water. Measurements of the optical density,  $E$ , were made at wavelengths of 5400 angstroms and 5600 angstroms on each diluted specimen. From the  $E$  values at these wave-

<sup>3</sup> Either the E. & J., or the Emerson Resuscitator.

<sup>4</sup> Furnished by the Linde Air Products Company.

<sup>5</sup> McKesson resuscitator.

lengths, Hüfner's quotient, the ratio,  $R = (E_{5400 \text{ AU}}/E_{5600 \text{ AU}})$  was calculated for each specimen and the corresponding percentage saturation of carbonylhemoglobin in the dilution examined was obtained.

The spectrophotometric method employed was essentially that devised by Hüfner (2) as modified by Ray, Blair and Thomas (3). We employed 0.2 per cent aqueous ammonia solution as the blood diluent to avoid the danger of pigment degradation which was observed when 0.4 per cent aqueous ammonia solution was used. In all instances our dilutions of blood examined have been 1:250, whereas other workers employed dilutions of 1:100 or 1:200. This difference in dilution, and the recognition that dilution of blood partially saturated with carbon monoxide with air-saturated ammonia solution, might be expected to produce a change in the percentage saturation of the carbonylhemoglobin present in the original blood sample, led us to consider a correction for possible dilution effect. However, our experiments to date have not borne out the necessity for such corrections.

Centrifuging the diluted blood solutions was found to be necessary although uncentrifuged solutions appeared to be clear on visual inspection. The suspended material present interfered with accurate spectrophotometric measurements. The use of other hemolyzing agents such as saponin was avoided, since saponin-treated bloods were found to develop degradation products rapidly, with consequent changes in absorption.

Other wavelengths in various portions of the spectrum of oxyhemoglobin and carbonylhemoglobin are practical for the spectrophotometric examination of blood solutions, notably those suggested by Heilmeyer (4), Kennedy (5), Horecker (6) and others, but for our purpose it was felt that they offered no special advantages over the well established 'Hüfner' points.

That the spectrophotometric method for the analysis of blood solutions containing oxygen and carbon monoxide yields results in close agreement with gasometric methods has been demonstrated by a number of workers in this field (4, 6).

## RESULTS

### *Blood Carbonylhemoglobin Content*

*Group I.* Eight dogs were exposed to 0.3 per cent CO in the gassing chamber until respiratory movements stopped. The average saturation of the blood with CO was 72.8 per cent, with a range of 62 to 79.5 per cent. At autopsy the animal with the lowest degree of saturation (62%) was found to be in an advanced stage of pregnancy; the fetal blood was 7.5 per cent saturated with carbon monoxide.

*Group II.* Twenty dogs, which were removed from the chamber after

the appearance of the first gasp for treatment but did not survive, had an average blood saturation of 73.2 per cent, with a range from 60.5 to 88.3 per cent.

*Group III.* Forty-one dogs which were successfully resuscitated had an average calculated saturation at the time of removal from the chamber of 74.3 per cent with a range from 64 to 83 per cent. Since at least one minute elapsed between the onset of air hunger and the first blood sampling, during which resuscitation was in progress, the first sample was not truly representative of the blood at air hunger. Hence, the initial blood was calculated by retrograde extrapolation from the first two samples obtained which were usually five minutes apart.

TABLE 1. PERCENTAGE OF CARBOXYHEMOGLOBIN IN BLOODS TAKEN FROM VARIOUS PARTS

DOG NO.	LEG VEIN	SPLEEN	PORTAL VEIN	LIVER	HEPATIC VEIN	RIGHT AURICLE	LEFT VENTRICLE
110	56.0	76.0	65.0	78.0	58.5	55.0	29.0
111	64.5	73.8	64.5	78.8	69.0	71.0	58.5
114	33.0 <sup>1</sup>	75.0	62.0	69.3	60.5	49.5	21.0
122		81.0	76.0	75.0	77.0	66.8	45.0
124		83.5	82.0	82.5	71.5	76.5	53.0
126			53.5	81.8	59.5	58.5	56.3
128		86.0	75.8	78.0	73.3	73.8	55.5
Ave.....	61.8	79.1	68.4	77.5	67	64.5	45.5

<sup>1</sup> 33 at 30 minutes.

*Group IV.* In 7 dogs in which resuscitation was unsuccessful, blood samples were taken from the portal and hepatic veins, the right auricle and the left ventricle, and also from the liver by pressing sections of that organ. The spleens were macerated, centrifuged, and the supernatant liquid was analyzed for carboxyhemoglobin. These data are presented in Table 1.

The livers and spleens had a high carboxyhemoglobin content, with an average of 77.5 per cent saturation for the former and 79.1 per cent saturation for the latter. The portal and hepatic veins had a very similar degree of saturation, averaging 68.4 and 67 per cent, respectively. The blood from the right auricle was only slightly less saturated, on the average, than that from the hepatic veins; the blood from the left ventricles, however, was much less saturated with an average value of 45.5 per cent.

### *Hemoglobin Concentration*

Undiluted blood samples drawn before the animals were exposed to the carbon monoxide-containing atmosphere were used for hemoglobin determi-

nations. These values were obtained by multiplying the  $E$  value observed on the diluted blood at 5400 angstroms by 250 (dilution factor) times 0.11971 (absorption coefficient in units of gm./100 cc.). In some cases, as a check determination the hemoglobin was determined from the  $E$  values of partially saturated blood, or on the basis of carboxylhemoglobin. Close agreement was found in such instances. Among the 41 surviving dogs the average hemoglobin concentration was 15.3 grams per 100 cc., with a range from 11.1 to 20.6. The values for the same number of nonsurvivors was found to be 14.5 gm./100 cc., with a range from 9 to 20.5.

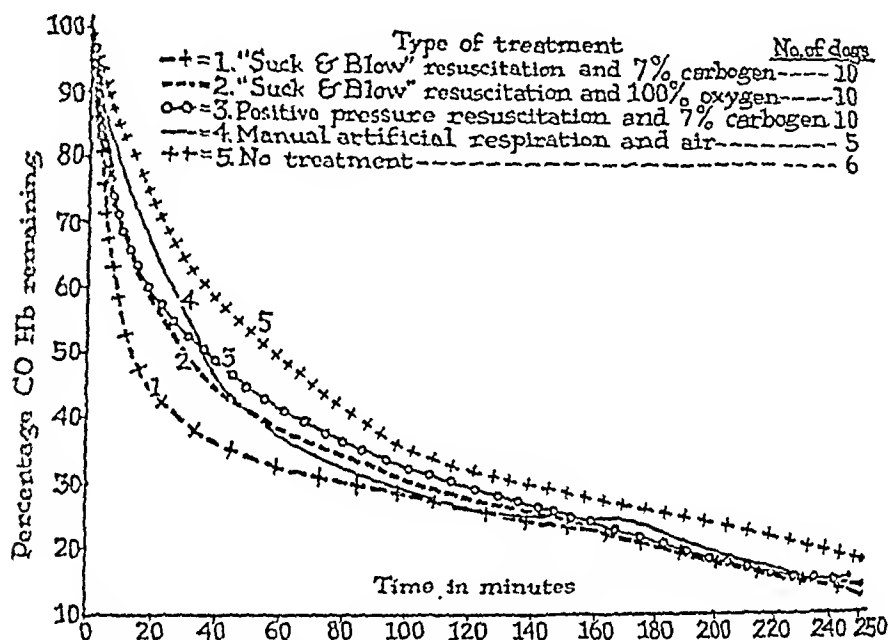


Fig. 1. ELIMINATION OF CARBON MONOXIDE from the blood of dogs.

### *Rate of Clearance of Carbon Monoxide*

The rate of elimination of carbon monoxide is shown in figure 1. These curves are based on the blood analyses derived from 41 dogs; 10 each in the groups resuscitated by mechanical devices, and 5 and 6, respectively, in those given manual respiration and no treatment.

Blood was drawn from the dogs at intervals of 5 minutes for 40 minutes, or as close to these intervals as was possible, and at intervals of 30 minutes thereafter for a total of 4 hours except in the dogs given no treatment, in which the initial intervals were 20 to 30 minutes.

To facilitate comparison between groups, all data were calculated in terms of percentage decrease of carboxylhemoglobin from the saturation existing at the time of removal, when treatment was begun. The saturation at this point was determined by retrograde extrapolation to zero time.

of the values found for the first two samples, it being kept in mind that the average carbon monoxide saturation of the blood was 74.3 per cent.

In the curves shown in figure 1 it is evident that the most rapid clearance of carbon monoxide from the blood was effected by oxygen—either 100 per cent or with an admixture of 7 per cent carbon dioxide—when administered with a mechanical resuscitator. When oxygen was not used, as in the other groups, the degree of saturation of the blood with carbon monoxide declined at an appreciably slower rate. Four hours after treatment was begun the blood of the dogs in all groups had approximately the same degree of saturation.

During the first 5 minutes the rate of elimination of carbon monoxide was similar in all three methods using oxygen. Thereafter there was a gradual decrease in clearance with the positive pressure apparatus, using 7 per cent carbogen (*curve 3*, fig. 1), and the 'suck and blow' type of apparatus, using 100 per cent oxygen (*curve 2*, fig. 1). With the latter type of device using 7 per cent carbogen, however, the initial rapid rate persisted for approximately 10 minutes longer (*curve 1*, fig. 1). At 20 minutes after the start of resuscitation the carbon monoxide saturation of the blood of the latter group was reduced to 48 per cent of that prevailing originally while in the other two groups it was reduced to 58 per cent.

Among the dogs resuscitated manually the decline in carbonylhemoglobin remained at approximately the same rate for the first 40 minutes, when 45 per cent of the original carbon monoxide was still present in the blood. From this point the rate was slower and similar to that in the groups treated with mechanical resuscitators.

The slowest decrease was found among the dogs given no treatment. Without aid the carbon monoxide was excreted more slowly but the rate of elimination approximated that of the other groups after nearly two hours.

It should be remembered that the duration of resuscitation treatment for each group was very brief. The 20 dogs resuscitated with 7 per cent carbogen were treated for periods ranging from 1 to 8 minutes, with an average time of 3.3 minutes. Treatment with 100 per cent oxygen was administered for 2 to 14 minutes, the average time being 4.2 minutes. Manual respiration was continued for periods of 3 to 5 minutes, for an average of 3.4 minutes.

#### DISCUSSION

In view of the excellent correlation between the average degree of saturation of the blood with carbon monoxide found in dogs allowed to die in the chamber (72.8 per cent), and that calculated to exist at the time the treated dogs were removed (76.3 per cent) the use of the latter as a basis for

the clearance curves is valid. Calculations for the initial carbon monoxide saturation were made individually for each dog.

No direct relationship was found between the concentration of hemoglobin present in the blood and the chances of survival in carbon-monoxide asphyxia. The average difference in hemoglobin values between the survivors (15.3 gm./100 cc.) and non-survivors (14.5 gm./100 cc.) is suggestive, but not significant, since individuals with high and with low hemoglobin concentrations were present in each group. An extreme anemia, however, predisposes to an inordinately rapid onset of air hunger; but within normal ranges of hemoglobin concentration it is without apparent significance, since we have observed that 2 dogs, which were exposed in the chamber simultaneously, arrived at the stage of air hunger at the same time, while subsequent blood determinations revealed hemoglobin values of 18.2 grams/100 cc. in one and 14.6 grams/100 cc. in the other.

The marked variation in the susceptibility to the effects of carbon monoxide asphyxia is evident from the data presented in table 2. Also, it is to be noted that the mean carbon monoxide saturation at the time of the first gasp is 74.3 per cent. The 20 dogs with a saturation of 74 per cent or less were exposed for an average of 52 minutes before they manifested the first gasp, whereas the 21 dogs with a saturation of 74 per cent or more withstood the exposure for an average of 76 minutes. These latter animals were obviously more tolerant to anoxia for some reason other than the hemoglobin content of the blood. The answer to this question is not evident in any of our data.

#### *Blood Distribution, Post-mortem*

The concentration of carbonylhemoglobin found post-mortem in the spleen in dogs on which resuscitation was unsuccessful was somewhat higher than the concentration present in the heart blood of dogs allowed to die in the chamber. The difference may not be significant, in view of the small number of dogs in each group, but there is a possibility of substances other than carbonylhemoglobin being a source of the higher values observed. This, however, is merely conjecture and more remote than if one assumes that a circulatory factor is involved.

The high degree of saturation with carbon monoxide of the splenic blood, which closely parallels that of the general circulation, is an indication that circulation through the spleen continues throughout the period of carbon monoxide asphyxia. According to De Boer and Carroll (7) the spleen contracts when the hemoglobin of the blood is 8 per cent saturated with carbon monoxide. At the carbon monoxide concentration used in our experiments the contraction must have occurred within several minutes after

gassing was begun, and it is probable the contracted state persisted, since at autopsy the spleen was invariably very small and hard. Since the splenic blood concentration of carboxylhemoglobin remained high while the carboxylhemoglobin in the blood of the heart and the peripheral veins showed a distinct decrease after resuscitation was begun, it is apparent that little if any blood was circulating through the spleen at this time. Although the spleen capacity is small in the contracted state, it is possible that the resumption of circulation through this organ with the consequent washing out of the erythrocytes saturated with carbon monoxide may account for some of the sudden aberrant rises in carboxylhemoglobin we observed during the later stages of carbon monoxide elimination in some animals.

In contrast to the spleen, the liver at autopsy was engorged with blood. Its carboxylhemoglobin content was likewise high and did not readily decrease with the beginning of resuscitation. Both the gross appearance and this high carboxylhemoglobin content and the fact that the blood entering and leaving the liver has a lower carboxylhemoglobin content point to a stagnant circulation, probably the direct result of the prolonged anoxia within the hepatic capillaries and sinusoids. Because of its large blood storage capacity, the liver is thus a potential source of carboxylhemoglobin for a considerable time after the resumption of normal respiration. This deduction has been confirmed experimentally by studies on the fate of carbon monoxide in the body during recovery from mild carbon monoxide poisoning in man (28).

Although none of the animals from which these samples were taken survived, it is evident from the difference in concentration of carboxylhemoglobin between the right and the left hearts that a varying degree of cardiac activity was present in all of them ante-mortem. A pulse which soon disappeared was palpable through the chest wall in only one of these animals. In one dog (no. 114, table 1), no pulse was palpable at any time during 30 minutes, although five blood samples were drawn without difficulty. From the carboxylhemoglobin determinations made on the blood from the right auricle and the left ventricle it is clear that the heart was functioning to some extent during the entire 30-minute period. This is corroborated by the carboxylhemoglobin concentration in the blood drawn from a leg vein at 30 minutes. This value of 33 per cent saturation corresponds to the average for the group to which this dog belonged. This tremendous decrease from 49.5 per cent to 21 per cent saturation with carbon monoxide of the blood during passage through the lungs is dependent upon a heart capable of maintaining an adequate circulation. With a feeble cardiac function a lesser amount of blood is exposed to the alveolar gases and less carbon monoxide is liberated into the alveolar spaces. The salutary effect of oxygen



in resuscitation from carbon monoxide poisoning is based in part on its ability to invigorate the failing myocardium, thereby increasing the cardiac output and promoting the elimination of carbon monoxide.

It has been known for many years that inhalation of oxygen is more effective than inhalation of air in facilitating the excretion of carbon monoxide. The early report of Grehan (8) to this effect was followed by confirmatory reports by Nicloux (9), Sayers and Yant (10), Walton *et al.* (11), Tervaeert and Bijlsma (12) and others. Henderson and Haggard (13), likewise found that the inhalation of oxygen was superior to the inhalation of air in facilitating the elimination of carbon monoxide, but they also found that a mixture of 10 per cent carbon dioxide in oxygen or in air was more effective than 100 per cent oxygen, and later (14) advocated the use of 5 per cent carbon dioxide in oxygen in conjunction with the prone pressure method of artificial respiration. Drinker (15) found this combination very effective in acute carbon monoxide poisoning. In 1929 Heller, Killiches, and Drinker (16) reported that 7 per cent carbogen was far more effective than 5 per cent carbogen as a respiratory stimulant, and Drinker and Shaughnessy (17) advocated the clinical use of the 7 per cent mixture.

Other investigators, however, were not convinced that the faster excretion of carbon monoxide produced by carbogen inhalation is of any material benefit. Sayers and Yant (10), who also found mixtures of 8 to 10 per cent carbon dioxide in oxygen more effective than 100 per cent oxygen, saw no advantage over the use of oxygen when time necessary for recovery after exposure is taken into consideration. Walton *et al.* (11) considered the slightly faster elimination afforded by carbogen of no particular advantage and recommended the use of pure oxygen because of its greater availability. Teleky (18) was of the same opinion. In our study (1) of the comparative effectiveness of 7 per cent carbogen and 100 per cent oxygen administered by mechanical resuscitators of the 'suck and blow' type, we were unable to show any difference between the two, when immediate survival and after effects are considered.

The clearance curves derived from our work are of the same type as those reported by Nicloux, Walton *et al.*, and Sayers and Yant, although our experiments differ from theirs in that we administered resuscitation for a few minutes only instead of the entire period during which blood samples were drawn. The 'suck and blow' type of resuscitator removed carbon monoxide from the blood faster with 7 per cent carbogen than with 100 per cent oxygen. The McKesson apparatus, which allows rebreathing, cleared the blood at approximately the same rate as the 'suck and blow' type with 100 per cent oxygen, even though 7 per cent carbogen was employed. This discrepancy is probably due to the short period during which the apparatus

was used—an average time of 3.3 minutes. It is possible that the rebreathing permitted by the positive pressure apparatus may have prevented the rapid fall of alveolar carbon monoxide which occurs in the 'suck and blow' type by virtue of the negative pressure that removes a substantial part of the respiratory gases during each cycle. The accumulation of carbon monoxide which probably occurred in the face-mask of the resuscitator during the time of treatment (average time = 3 minutes) was apparently inadequate to increase the blood carbon dioxide level to the point of stimulating the respiratory center, which was still at a low functional level from the persistent hypoxia.

It is noteworthy that the effect of the carbogen in the dogs resuscitated with the 'suck and blow' type of apparatus persisted for some time after cessation of treatment. This phenomenon is probably due in large part to an increased depth of respiration, since von Oettingen *et al.* (19) observed an increased respiratory volume for several hours after the administration of 6 per cent carbogen. On the other hand, Murphy and Drinker (20) found that in the juxta-lethal stage of carbon monoxide asphyxia neither 5 per cent nor 10 per cent carbogen was effective in stimulating the respiratory center, although 10 per cent evoked some response in a less advanced stage and both 5 per cent and 10 per cent were effective during the early stages. This apparent insensitivity of the respiratory center may be due to a species difference, since their work was done on cats.

Another factor worthy of consideration is the acceleration of dissociation of the carbonylhemoglobin caused by the carbon dioxide, as demonstrated *in vitro* by Douglas, Haldane, and Haldane (21), and *in vivo* by Stadie and Martin (22). The latter also obtained an increased elimination of carbon monoxide by the intravenous injection of hydrochloric acid and concluded that the increased acidity was responsible. However, their experimental conditions did not simulate those of acute carbon monoxide poisoning in which there is developed a metabolic acidosis and a consequent reduction of blood  $pH$  (23-27). Stadie and Martin reported blood  $pH$  values of 7.34 and 7.38 at the beginning of treatment with hydrochloric acid and 10 per cent carbogen, with a subsequent decrease in  $pH$  parallel to the increase in excretion of carbon monoxide. Yant *et al.*, however, reported  $pH$  determinations at death from CO asphyxia of 21 to 30.5 minutes duration, ranging from 6.88 to 7.25, and it is difficult to understand how, in such a degree of acidosis which presumably prevailed when the animal was in a resuscitable state, a further increase in acidity, assuming it could result from inhalation of 7 per cent carbogen, could facilitate the dissociation of carbonylhemoglobin.

According to Henderson and Haggard (14) the inhalation of a carbon

dioxide-air mixture produced a more rapid clearance of carbon monoxide than inhalation of oxygen. Other investigators (9, 11) have been unable to confirm this observation. The basis for the insistence of these workers upon the necessity for carbon dioxide is probably the observation, made on a few dogs, that the respiration after carbon monoxide asphyxia is too feeble to ventilate the lungs efficiently and that the elimination of carbon monoxide at this time is very slight. During our observations on several hundred dogs (1) asphyxiated with carbon monoxide, we have seen many animals gasping vigorously when the blood carbonylhemoglobin content was between 64 and

TABLE 2. CARBON MONOXIDE SATURATION OF THE BLOOD IN FORTY-ONE DOGS AT THE FIRST GASP OR MANIFESTATION OF AIR HUNGER, ALL SURVIVING RESUSCITATION

DOG NO.	TIME OF EXPOSURE	INITIAL CO SAT.	DOG NO.	TIME OF EXPOSURE	INITIAL CO SAT.	DOG NO.	TIME OF EXPOSURE	INITIAL CO SAT.
	min.	%		min.	%		min.	%
244	135	64	74	29	72	135	27	78
263	98	64	248	160	73	223	95	78
123	30	66	258	88	73	58	28	79
264	44	66	109	36	73	125	39	80
115	25	67	213	65	73	131	48	80
207	81	67	284	51	74	82	27	80
85	34	67	220	93	74	81	28	81
114	56	68	73	53	74	260	104	82
276	98	68	259	87	75	105	50	82
210	100	68	217	89	75	76	22	82
282	158	69	129	42	76	78	21	82
227	35	69	218	91	76	55	17	82
108	107	71	233	31	76	54	42	83
219	91	71	71	61	76			

Average time of exposure of the 20 dogs with carbon monoxide saturation of 74 or less was 52 minutes; of the 21 dogs with carbon monoxide saturation of 74 or more, 76 minutes.

Average carbon monoxide saturation of these 41 survivors is 74.3%, range 64 to 83%.

Average carbon monoxide saturation of 28 non-survivors 73.1%, range 60 to 88%.

84 per cent. Eight of 22 dogs which were given no treatment except removal from the carbon monoxide-containing atmosphere were able to survive by virtue of their own respiratory efforts. The elimination curve of 6 of these dogs (fig. 1) shows that they were able to eliminate 50 per cent of the carbon monoxide in the blood within 60 minutes. These data are in accord with those of Walton *et al.* and Nicloux, but differ markedly from those of Henderson and Haggard (14), whose clearance curves for untreated dogs shows a decrease of less than 15 per cent within 60 minutes. The latter authors also found that after 60 minutes of inhalation of oxygen, only 37 per cent of the carbon monoxide had been eliminated from the blood. In contrast, the analogous determinations of Nicloux and of Walton *et al.*

were 87 per cent and 90 per cent, respectively, while our curves—based on animals treated for an average of 4.2 minutes with oxygen—show that 60 per cent was eliminated within 60 minutes. It is obvious that the inhalation of oxygen is an efficient means of reducing rapidly the carbon monoxide content of the blood.

• With the aid of manual artificial respiration, surviving dogs breathing air were able to eliminate carbon monoxide faster than those unaided, but at a considerably slower rate than those treated with oxygen. This assistance was ineffective in increasing the survival ratio to any significant extent, for only 10 of 20 dogs survived. The inability of carbon dioxide to increase further the number of survivors is demonstrated in another group reported in another paper (1) in which the dogs were given manual respiration with the inhalation of 7 per cent carbogen; only 13 of 30 survived.

In our study (1) on the efficacy of several methods of resuscitation from acute poisoning with illuminating gas, of which the dogs reported in the present work are a part, we came to the conclusion that mechanical artificial respiration using either 100 per cent oxygen, or 7 per cent carbogen, was the most effective method. Since the survival ratio with 7 per cent carbogen was not significantly different from that with 100 per cent oxygen the slightly greater rapidity of elimination of carbon monoxide induced by the former is of no practical significance, in regard to survival and the incidence and severity of neurological sequel. The rôle of carbon dioxide in resuscitation from asphyxia has been exaggerated by those who advocate the use of the prone pressure method, which to be useful requires the aid of a respiratory stimulant. Modern mechanical resuscitators which deliver oxygen into the lungs at an effective, but not dangerous, pressure do not require the aid of carbon dioxide, and in our experience have proved to be appreciably more effective in resuscitating acutely poisoned dogs than manual methods.

If administration of oxygen is to be effective it must be delivered in adequate quantity to the alveolar spaces from which it can be rapidly absorbed by the blood. The obvious prerequisite is a functioning heart, for unless the blood is circulating, oxygen in the lungs is of no value. Normally, the blood carries 0.5 cc. of oxygen per 100 cc. in physical solution but when the oxygen tension in the alveolar space is increased, more oxygen is dissolved, so that the administration of 100 per cent oxygen elevates the plasma oxygen content to 2.5 per cent. Oxygen dissolved in the plasma is in its most available form; when it arrives at the capillaries its passage into the tissue fluids and cells is immediate, especially so when it is under abnormal tension and when the tissues have been subjected to anoxia. In carbon monoxide poisoning the administration of oxygen fulfills another

important function: it forces the dissociation of carboxylhemoglobin and thereby promotes the rapid elimination of carbon monoxide.

With a heart still functioning, although enfeebled by the prolonged anoxia, and a high oxygen tension in the alveoli, it is evident that the first organ to receive the newly oxygenated blood is the heart. After passage through the left ventricle a part of the blood enters the coronary circulation where it will either invigorate the faltering myocardium and thus augment the systemic circulation, or it will have no effect because the pathological changes within the myocardium are irreversible. If the rehabilitation of the heart is successful, a salutary cycle is initiated, which simultaneously effects a rapid elimination of carbon monoxide and a restoration of oxygen supply to the hypoxic tissues. Respiratory movements return when the extreme anoxia of the brain stem is alleviated and the formation of endogenous carbon dioxide attains stimulatory levels.

### CONCLUSIONS

The only effects of the administration of exogenous carbon dioxide are the slightly more rapid excretion of carbon monoxide and, in some cases, a more rapid restoration of respiratory movements. The significance of these effects has been exaggerated, while the much greater significance of adequate cardiac function has in large part been overlooked. Since carbon dioxide plays no demonstrable part in fortifying cardiac function and its addition to oxygen confers no further value in resuscitation, the inevitable conclusion is that it is an unnecessary therapeutic adjunct.

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# Cardiac Stimulation in Carbon Monoxide Asphyxia<sup>1</sup>

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THE POSSIBILITY that death from carbon monoxide asphyxia is primarily the result of cardio-vascular failure renders it desirable to investigate the effect of cardiac stimulants as an adjunct to other resuscitation procedures. This is a subject which has been discussed frequently for and against, but definitive experimental evidence has not been submitted. This report is concerned with our experimental attempts to resuscitate dogs asphyxiated with 0.3 per cent CO, one minute after the last respiratory gasp, with a combination of intra-cardiac medication and mechanical resuscitation using 100 per cent oxygen.

## METHODS

Forty-five apparently normal dogs of both sexes, weighing from 5 to 10 kg., were exposed singly, or in pairs, to diluted illuminating gas (0.3% CO) which was flowing through a closed chamber at a rate of 195 liters per minute. The animals were observed closely for the onset of the spasmodic respiratory gasps characteristic of air hunger. Exactly 50 seconds after the last gasp the dogs were removed from the chamber and 10 seconds later the treatment was begun.

Each of the 45 dogs was treated with 100 per cent oxygen administered with an alternating positive and negative pressure resuscitator (E & J Resuscitator). *Group A* or 15 of them received no other treatment. *Group B* or a second group of 15 were given 1 mg. of epinephrine hydrochloride and 0.65 mg. of atropine sulfate in 1 cc. of normal saline injected into the heart with a 19-gauge spinal needle. *Group C* or a third group of 15 were given 1 cc. of 0.85 per cent NaCl also intra-cardially.

Observations were made on the presence and character of the pulse, before and after injection, by palpation of the chest and feeling through the needle used for intra-cardiac injection. Resuscitation was continued for a minimum of five minutes on the dogs in which cardiac pulsation and respiratory movements did not return immediately. The dogs which responded to treatment were given oxygen by the mechanical resuscitator until they were able to breathe without its aid.

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## RESULTS AND DISCUSSION

The results are summarized in the tables.

The data in table 1 show that the intra-cardia injection of epinephrine and atropine is an effective aid to the mechanical resuscitation of dogs which have neither pulse nor respiratory movements as a result of acute CO asphyxia. Although cardiac activity was stimulated in 4 animals by the injection of 0.85% NaCl, it was of brief duration and no animal so treated

TABLE 1. SHOWING THE EFFECT OF EPINEPHRINE AND ATROPINE ON THE SURVIVAL RATIO WHEN ADMINISTERED ONE MINUTE AFTER THE LAST GASP INTRACARDIALLY

TREATMENT (OTHER THAN OXYGEN)	NO. DOGS	TIME EXPOSED		APICAL PULSE		NO. OF DOGS	
		Range	Average	Before injection	After injection	Surviving	Not surviving
		minute	minute				
<i>Group B</i> Epinephrine & Atropine	15	31-136	59.5	0	4	4	11
<i>Group C</i> 0.85% NaCl.	15	29-91	51.3	0	4	0	15
<i>Group A</i> None	15	28-98	54.4	3		0	15

TABLE 2. SHOWING BEHAVIOR OF THE SURVIVORS DURING AND AFTER THE RESUSCITATION

DOG NO.	PULSE		RESPIRATION BEGAN IN	SURVIVAL TIME	PATH. CHANGES IN HEART
	Time of appearance	Character rate			
1	At injection	Vig. reg. 240	12 min.	68 hr.	1 cc. blood in pericardium
2	1 min. after	Vig. reg. 232	11 min.	36 hr.	4.8 cc. blood in pericardium
3	1 min. after	Mod. reg. 180	34 min.	16 hr.	5.6 cc. pericardial fluid
4	10 sec. after	Vig. reg. 216	12 min.	30 days	Not examined

survived. The mechanical stimulation of the needle prick may have been the cause of the resumption of the cardiac contractions, but it is noteworthy that in only those animals which were given epinephrine and atropine was it possible to maintain the cardiac activity and subsequently restore the respiratory movements.

The behavior of the 4 surviving dogs during and after resuscitation is summarized in table 2. The response to the injection was immediate in only one animal. In the other 3 dogs the delayed response suggests that the injected fluid and not the needle puncture was the stimulus since the response to the latter would be expected to be immediate. It is possible,



however, that the response to the stimulus was initially too weak to be perceptible to palpation and became perceptible only after the heart had developed a more vigorous stroke. Among the dogs treated with NaCl, one manifested intermittent beats three minutes after injection, while in 3 others the response was immediate but did not persist.

Although the cardiac activity in the surviving dogs appeared within a short time after injection an inordinately long period of mechanical resuscitation (11-34 minutes) was necessary before endogenous respiratory movements were strong enough to maintain an adequate minute volume. This is undoubtedly the result of the long anoxic period preceding the resuscitation attempt, since it was shown (1) that if mechanical resuscitation with 100% oxygen is begun at the onset of air hunger the average period of treatment necessary is less than five minutes. Thus it is apparent that in the absence of either pulse or respiratory movement following acute CO asphyxia the restoration of the pulse is of primary importance and that once this has been attained respiratory movements can be restored if mechanical ventilation of the lungs is continued. It is clear that the reverse order of restoration will not occur, since the respiratory center is reactivated by the resumption of its oxygen supply, which is palpably impossible in the absence of cardiac function.

The deleterious effect of prolonged anoxia on the central nervous system is demonstrated by the post-resuscitation history of the 4 surviving dogs. Three died within less than 68 hours; the fourth was apparently normal 30 days after resuscitation, but it suffered a transient episode of moderate ataxia and anorexia which began on the third day after treatment and lasted about 10 days. Two of the dogs remained comatose until death occurred at 68 hours and 16 hours. The remaining dog, which suffered complete paralysis of the hind legs, died after 36 hours. On post-mortem examination a small quantity of bloody pericardial fluid was found in 2 dogs, while in the third 5.6 cc. of colorless fluid was found. This pericardial effusion, which was found in the dog which survived only 16 hours, is probably the result of the prolonged anoxia since a similar finding has been reported in many dogs which could not be resuscitated after acute CO asphyxia (1).

The behavior of this dog (dog 3, table 2) affords an excellent demonstration of the importance of the intrinsic cardiac condition as the determining factor in the success or failure of resuscitation. This animal had no pulse when treatment was begun, one minute after the last gasp. A regular pulse of moderate strength became palpable one minute after the intracardiac injection and persisted for 16 hours. But respiratory movements

were inadequate to maintain ventilation until 34 minutes after the treatment was begun.

We have been unable to find any reports of previous experimental cardiac resuscitation after carbon monoxide asphyxiation. Crile and Dalley (2) reported resuscitation of asphyxiated dogs by injection of epinephrine into the femoral artery toward the heart, but they do not describe the method of asphyxiation. They found that animals were more easily resuscitated after death from ether and chloroform than after death from asphyxia. Resuscitation, if successful, occurred within one minute after administration of epinephrine and artificial respiration in the majority of instances, rarely after an interval of three minutes. They were able to resuscitate animals readily and uniformly up to five minutes after death; death was considered to be the moment when all vascular pulsation ceased, the blood pressure was 0, and the heart sounds were inaudible. They concluded "the probable success of resuscitation is greater in inverse proportion to the lapse of time after death; a rapid rise in the arterial pressure is attained by arterial infusion with a therapeutic dose of adrenalin, together with good artificial respiration and the avoidance of unnecessary cardiac trauma by massage. All artificial aids should cease as soon as the functions are competent."

In 1921 Gunn (3) advocated the injection of epinephrine into the jugular vein and the pericardial sac in cases of cardiac arrest due to chloroform. In animal experiments he revived the heart in this manner while maintaining artificial respiration with bellows 5 to 10 minutes after cardiac arrest. He advocated the injection of atropine intravenously after the heart began to beat regularly and strongly. He found that natural respiration began 5 to 10 minutes after the heart began to beat, but was sometimes delayed up to 30 minutes. When treatment was begun within 10 minutes after complete cardiac arrest he was able to resuscitate 70 per cent of the animals.

It is stated by Hyman (4) that the mechanical stimulation resulting from cardiac puncture alone is responsible for resumption of cardiac activity. Our experiments demonstrate that the intracardiac injection of 0.85 per cent NaCl does stimulate the heart arrested by carbon monoxide asphyxia but the effect is transitory. It is evident that a needle puncture is inadequate even though it remains as a focus of irritability; apparently a repeated or persistent stimulation is necessary.

According to Danielopolu and Marcou (5) the asphyxiated heart is much less sensitive to adrenalin than the normal heart. Under normal conditions adrenalin in therapeutic doses is amphomimetic, but predominantly sympathomimetic and produces an increase in cardiovascular tone. During

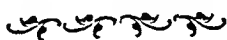
cardiac asphyxia the sympathetic influence decreases and at a certain dose the parasympathetic effect is so pronounced as to inhibit the heart. The injection of epinephrine alone is ineffective in restoring cardiac activity. To counteract the deleterious parasympathetic action they advocate the intra-cardiac injection of atropine prior to the injection of epinephrine.

#### SUMMARY

We observed that the intra-cardiac injection of epinephrine and atropine in conjunction with oxygen administered by a mechanical resuscitator was effective in resuscitating 4 of 15 dogs asphyxiated with carbon monoxide when treatment was begun one minute after the last gasp and no cardiac impulse was palpable. Under the same conditions the injection of 0.85 per cent NaCl was ineffective in 15 dogs, although it did induce a transitory cardiac activity. In view of these observations it is probable that this treatment is worthy of trial as a last resort in human cases of cardiac arrest following carbon monoxide asphyxia.

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# *Application of the Infra-red Analyzer to the Study of Human Energy Metabolism*

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**S**TUDY OF HUMAN ENERGY METABOLISM by the indirect method of respiratory gas analysis has been thoroughly standardized in the research laboratory (1). Determination of the caloric expenditure of men under non-laboratory conditions as, for example, that of troops on maneuvers, has been less satisfactorily accomplished. The method used has been the classical Douglas bag Haldane analysis technique (2). The disadvantages of the method are *a)* only brief average samples of subject activity may be taken, *b)* accuracy of measurement depends upon the training and experience of the analyst and *c)* the apparatus is bulky and not adaptable to many physical situations.

It was our purpose in the present investigation to adapt recently developed electronic gas-analyzing apparatus, capable of detecting carbon dioxide, to metabolic measurement, and with the new techniques to obtain more accurate evaluation of non-laboratory energy expenditures. We have sought, first, a physical method of analysis for carbon dioxide, second, instantaneous continuous recordings rather than averaged values for short sampling periods and, third, portable equipment capable of measurement of energy expenditure under actual rather than simulated exercise conditions. The techniques have proved applicable to both laboratory and field investigation. The method with typical results is presented.

## METHODS

For the measurement of carbon dioxide concentration of expired air to be useful as a measure of metabolic expenditure, one of two conditions must be filled. First, the expiratory volume can be measured, from which the carbon dioxide concentration can be expressed as percentage by volume, as in the classical Haldane technique; or, secondly, the volume flow past the subject can be kept essentially constant by force pumping. Enrichment of this constant volume with carbon dioxide from expired air will permit ex-

pression of carbon dioxide as percentage of a flow. From data of this sort carbon dioxide, expelled by the subject for a period, can indicate directly his rate of production, regardless of the actual expired volume. We have utilized the latter principle. A schematic diagram of the assembly is given in figure 1.

A constant volume of air, exceeding in amount the maximum respiratory volume, was drawn past the subject by the main-line pumping system. An analyzer aliquot was drawn from this main flow by means of a small, constant speed rotary pump. In practice, the only limiting factor on maneuverability of the subject in reference to analyzer and recorder was the length

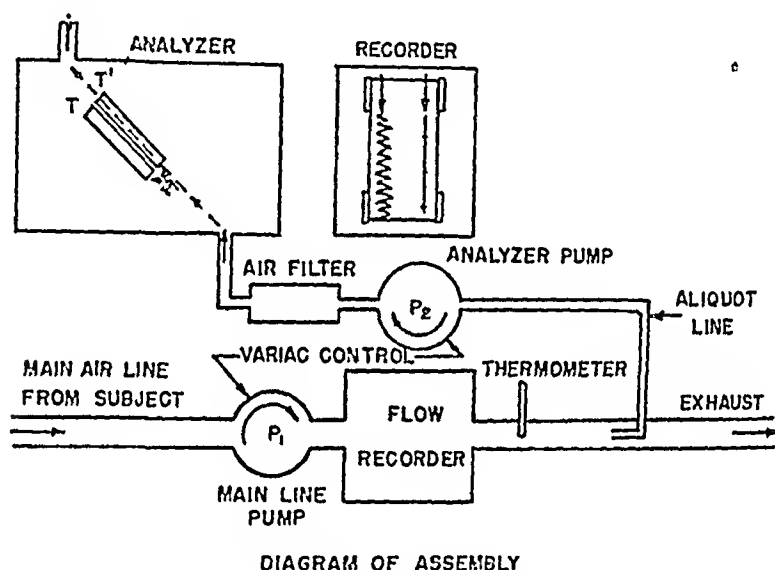


Fig. 1. SCHEMATIC DIAGRAM of air pumping system and analyzer assembly.

of air hose between subject and machine. The limit on this length was the ability to handle the hose mechanically. By use of cable and pulley rigging in the field, up to 400 feet of hose were handled with no more inconvenience to the subject than the usual laboratory mask assembly. In the laboratory, during standardization of the apparatus, various flow meters, mixing chambers, temperature baths and filtration columns for investigation of factors influencing instrument sensitivity and selectivity were inserted between the subject and the analyzer.

The Leeds and Northrup selective gas analyzer was designed to measure small concentrations of carbon monoxide (4). It has been adapted to quantitation of water vapor (5) and has been sensitized to carbon dioxide (3). The subject instrument is functionally based upon the selective absorption by the gas in question of radiation in the infra-red region of the spectrum (CO 4.7, H<sub>2</sub>O 6.0 and CO<sub>2</sub> 4.3 microns wave length absorption bands). A

complete technical description of the instrument, with detailed operating instructions, has been previously reported (4).

This analyzer, sensitized for carbon dioxide detection and equipped with an adequate pumping system for controlled air flow, was adapted to metabolic work. The A-13 oxygen demand mask was used in conjunction with long air lines. Air, drawn through the mask in constant volume by the pumping system, was enriched by expired carbon dioxide from the subject. This carbon dioxide was quantitatively detected and recorded by the gas analyzer. The method gave instantaneous analysis and continuous records over protracted periods. The determination of air-flow rates in the main and aliquot circuits was very accurately accomplished because subsequent carbon dioxide concentrations were interpreted as percentage of a constant volume. The volume flow of air through the large hose circuit past the subject depended upon the operating speed of the main line pump and the resistance induced by man, mask and flow meter. Arbitrarily a flow rate of 102 liters per minute was chosen. This rate was in excess of any minute volume flow subsequently obtained past a subject. It was achieved by a variac setting of 50 volts (P<sub>1</sub>, fig. 1) and standardized against a calibrated 500-liter capacity-recording laboratory spirometer. The small aliquot circuit leading to the gas analyzer was powered by a constant speed motor air pump designed to deliver about 10 liters of air per minute through the analyzer chamber. To check constancy of flow of this pump, the airstream was calibrated against the spirometer. Modification of the rate of air flow was obtained by adjusting the current supplied to the pump. This regulation was achieved with a 'variac' voltage control unit (P<sub>2</sub>, fig. 1), and tracings of volume versus time at various voltage settings recorded. For settings ranging from 40 to 160 volts the flow output varied between 10.02 and 12.00 l./min. The motor was designed to operate most efficiently at 120 volts. The air-flow rate at this setting was 10.87 l./min. This value was used throughout for aliquot line flow. Changes in flow of the main line had no effect on the constancy of the aliquot flow.

After air volume control was established, standardization of the infra-red gas analyzer against known carbon dioxide-oxygen gas mixtures was accomplished. An investigation of the factors influencing receptivity and interpretation accuracy of the instrument was undertaken.

*Standard Carbon Dioxide Mixtures.* Known mixtures of carbon dioxide and oxygen covering the expected range of carbon dioxide concentration (0-5%) to be encountered were prepared. These, with outside air (0.03% CO<sub>2</sub>) and pure oxygen, comprised the standard series. Air dilution at the source to 100 l./min. was enough in excess over expiratory volume to insure

analysis within this standard range. The standard gas mixtures were fed directly into the aliquot line to the analyzer. As stated, air flow to the analyzer was supplied at a constant rate of 10.86 l./min. Inserted into the air line between the pump ( $P_2$ , fig. 1) and the analyzer was a 'Charcolite' air filter (fig. 1). This served three purposes: *a*) mechanical filtration of air,

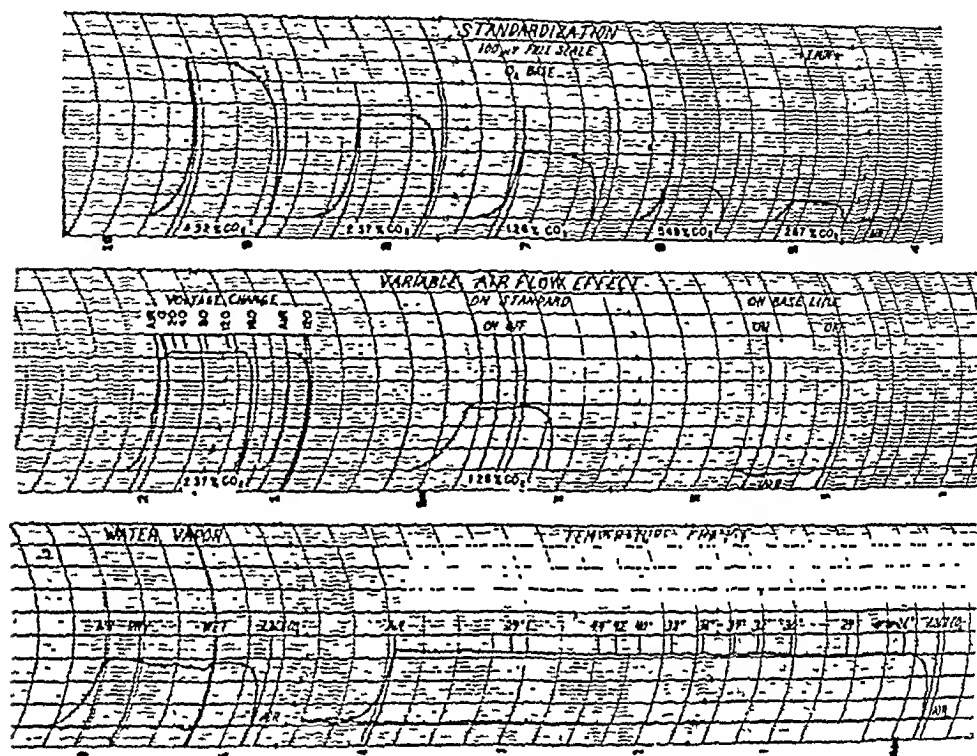


Fig. 2. ESTERLINE-ANGUS MILLIAMMETER recordings of experimental data, showing standardization curves and the effects of various factors on instrument sensitivity.

TABLE 1. STANDARD  $\text{CO}_2$  MIXTURES, MICROVOLT DEFLECTION

PERCENTAGE $\text{CO}_2$	AVERAGE MICROVOLTS	MAXIMUM MICROVOLTS
Oxygen (pure) . . . . .	0.0	0.0
0.267 . . . . .	6.95	7.8
0.549 . . . . .	15.1	17.0
1.260 . . . . .	33.5	37.0
2.370 . . . . .	51.2	57.0
4.320 . . . . .	77.0	82.0

*b*) removal of water vapor and *c*) removal of charcoal-absorbable gases. An initial series of responses of the gas analyzer to the various carbon dioxide mixtures is shown in figure 2. The Esterline-Angus graphic records read from right to left. Tabulation of the results in terms of average and maximum microvolt deflection is given in table 1. Average values were obtained by measuring the area under the curve for the entire period during which the test gas was running. This value, divided by the length of record, gave

the average deflection for the period. Averages are lower than the maximum recorded deflections because time of  $\frac{1}{2}$  to 1 minute was required to flush the test chamber completely on changing from oxygen to a carbon dioxide mixture. Ideally, both maximum and average values should have been identical; practically, the average value was of greater use for measurement of expired carbon dioxide.

*Oxygen Versus Outside Air (0.03% CO<sub>2</sub>).* Operation of the continuous-gas analyzer over extended periods required repeated standardization of the base line because of electrical drift in the recording meter. This base-line adjustment could have been made using cylinder oxygen, but in field work it was more convenient to standardize against outside air. A series of analyses was run; a) to measure the sensitivity of the machine to the 0.03 per cent CO<sub>2</sub> of air and b) to make direct comparison of standard mixtures using oxygen and air base lines. The average deflection produced by 0.03 per cent CO<sub>2</sub> was slightly greater than one microvolt. The response is recorded in figure 2. Comparison of the response of the machine to the known gas mixtures using the two base lines showed that deflection response of the machine to carbon dioxide versus oxygen was slightly greater than response to the same carbon dioxide versus air. The effects were within the anticipated range for purely additive values, that is 1 to 2 microvolt increase at each level. Curves comparing these responses are given later (fig. 3).

*Flow Change and Pressure Effects.* The apparatus was designed to give constant air flow to the analyzer but to ascertain just what effects changes in rate of flow through the analyzer cell would have on the readings, a series of experiments was conducted. The effect of sudden complete cessation of flow and of gradual decrease in flow was tested at the very low and at relatively high concentrations of carbon dioxide (0.03, 1.26 and 2.37%). Using the lowest concentration of gas (0.03% CO<sub>2</sub>), the following results were obtained: sudden stoppage of flow caused a fall in deflection of one microvolt practically instantaneously; on return of the flow, there was a reestablishment of the original deflection within  $\frac{1}{2}$  minute; prolonged stoppage of flow (2 minutes) produced a decrease in deflection of one microvolt within  $\frac{1}{2}$  minute, then a gradual fall of one microvolt over the succeeding 1.5-minute period; return of flow returned the deflection to its original level within  $\frac{1}{2}$  minute. Similar effects were seen with the higher concentrations of carbon dioxide: at a level of 1.26 per cent CO<sub>2</sub>, stoppage of flow caused a decrease in deflection of 2 microvolts within one minute; restoration of the previous level (29 microvolts in this case) required a little longer, 1 instead of  $\frac{1}{2}$  minute. Gradual cessation of air flow was difficult to evaluate because with a constant speed motor variation from 12 to 10 l./min. was the maximum maintainable (160 to 40 volts). Within this range no change in deflection



toward 2.3 per cent  $\text{CO}_2$  could be shown. At a variac setting of 20 volts, the motor failed after a short period of 5 l./min. flow. During this period a fall of 3 microvolts occurred. The fall was probably identical with the effect of cessation of flow. All of the preceding data are illustrated in the second record of figure 2.

*Temperature Effects.* Previous work with the infra-red machine, when used for analysis of carbon monoxide, indicated that recordings were stable

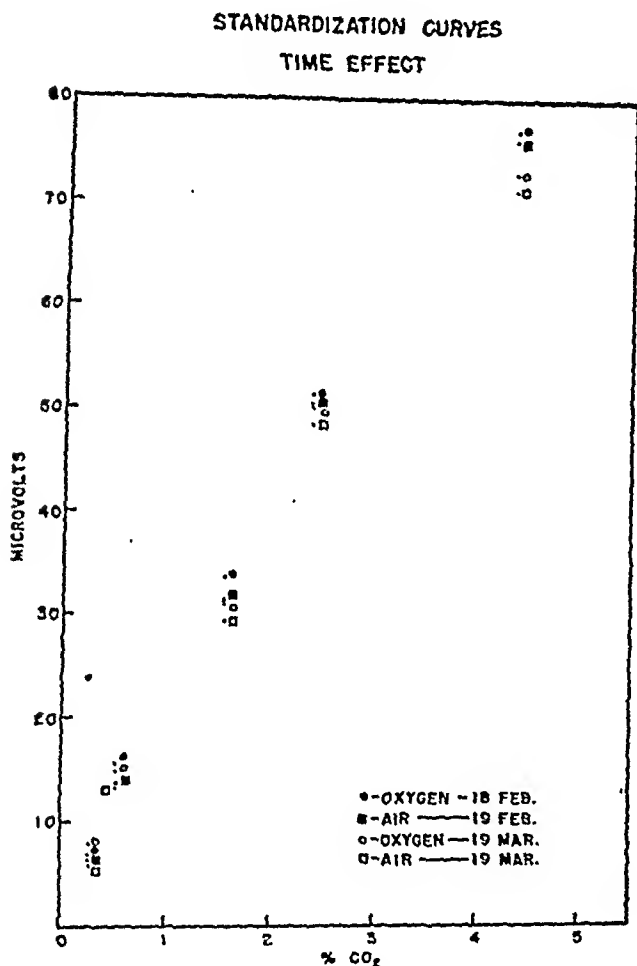


Fig. 3. VARIATION OF RESPONSE of the instrument to standard carbon dioxide mixtures with elapsed time.

under gradual changes of temperature. Nelson's report (4) implied a warning to avoid sudden temperature change, although no commitment was made as to the magnitude of the error introduced. The influence of temperature change on carbon dioxide analysis has been investigated. Warm-up of the machine for  $1\frac{1}{2}$  hours as recommended led to an analysis chamber temperature of  $30^{\circ}\text{C}$ . This temperature was maintained constantly while operating with ambient air of from  $26^{\circ}$  to  $29^{\circ}\text{C}$ . Preheating ingress air only slowly influenced the stabilized chamber temperature. Preheating inflowing air

from 26° to 44°C. during a period of 15 minutes increased the analysis chamber temperature from 30° to 33°C. The 3° rise in chamber temperature gave a maximum upward deflection of 4 microvolts. The recording pen was stationary between 30° to 31°C., rose one microvolt between 31° to 31.5°C., 2 microvolts between 31.5° to 32°C., 3 microvolts between 32° to 32.5°C. and reached a 4-microvolt rise at 33°C. Gradual increase in operating temperature caused the same positive deflection of the recorder pen for 1.26 per cent CO<sub>2</sub> as for air. This deflection can be attributed to a shift in the base line. Sudden change of inflow gas from 44° to 29°C. had no effect on the record. The only explanation of this fact is a lack of sensitivity of the instrument to sudden temperature change, because the gas passing through the analyzer was not heated to chamber temperature. Esterline-Angus experimental records of these data are given in figure 2.

*Effect of Water Vapor.* The influence of water vapor upon carbon dioxide analysis was small, transitory and self-compensating. Air at 27°C. saturated with water vapor caused an immediate downward displacement of the base line of approximately 2 microvolts. The effect was of 20 seconds' duration, then the record reassumed its base line. With carbon dioxide mixtures, a similar but exaggerated downward shift occurred. Using a standard mixture containing 1.26 per cent CO<sub>2</sub>, saturation with water vapor caused a downward displacement of 3 microvolts which lasted 30 seconds, then decreased in effect until the original deflection was regained after 2 minutes. Dry gas replacing the moist which had reached balance caused no shift in deflection. The effects are probably not those of interference with flow because the time elapsed in converting one mixture to another was very short. In addition, the immediate effects were greater than those produced by even prolonged flow stoppage. No flow change effect took place on converting from moist to dry gas. Records of these data are given in figure 2.

*Elapsed Time on Response.* Several factors have been reported by Nelson and other investigators as influencing the stability of the gas-analyzer response to standard gas mixtures. The instrument has been regarded as satisfactorily stable if precautions have been taken to assure: a) adequate warm-up, b) well-charged batteries, c) frequent zero adjustment of the established base line and d) occasional standardization against a known gas mixture. The most likely factor to account for change in response has been stated to be an electrical leakage from terminals to ground. In those instances in which there has been a distinct loss of sensitivity with elapsed time, the fault has been attributed to leakage of the filter cone (4). A mechanical sensitivity control for the instrument has been incorporated

so that one can adjust receptivity to a definite standard value. Duplication of standard curves by this means has been the practical way of controlling sensitivity loss (3).

During the accumulation of the following data, the sensitivity adjustment of the instrument was fixed in order to ascertain the absolute magnitude of inherent instrument-sensitivity loss. Standardization curves taken at different times using both oxygen and air base have been run. Comparative curves for each series are given (fig. 3). There was a loss of sensitivity during the 30-day period studied which was greater than casual variation between standardizations. There is insufficient evidence to attribute this loss to cone leakage on other than presumption from earlier reports. The practical method of adjustment of instrument sensitivity to a standard deflection with a known calibrating gas mixture nullifies the sensitivity loss.

TABLE 2. CALIBRATION DATA FOR CURVES OF MARCH 19

CONC. CO <sub>2</sub>	OXYGEN			AIR		
	E	K <sub>1</sub>	K <sub>2</sub>	E	K <sub>1</sub>	K <sub>2</sub>
%						
0.267	7.70	7.90	103	5.76	11.2	107
0.549	14.7	8.21	103	13.7	9.21	107
1.26	31.1	8.08	103	29.3	9.08	107
2.37	50.0	8.04	103	48.4	9.07	107
4.32	72.8	8.10	103	71.2	9.08	107

*Calibration of Curve.* The average deflection represented by each point in figure 3 was arrived at by measurement, in square millimeters, of the area under each tracing during the test period. From this value, average deflection in millimeters was calculated. Each 10-microvolt deflection on the recording paper represented 11.5 millimeters. From these data the equation for standardization was obtained. All curves conformed to the general equation:  $C = K_1 \log \frac{K_2}{K_2 - E}$  where, C = CO<sub>2</sub> concentration in per cent;

K<sub>1</sub> and K<sub>2</sub> = empirical constants and E = the microvolt deflection. Equation values for the curves of March 19 are tabulated in table 2.

In the above table, constant K<sub>1</sub> after establishment of K<sub>2</sub> should have been unchanged with variation of C and E within the individual series. Values at the higher concentrations of carbon dioxide, 1.26 per cent through 4.3 per cent, closely approached theoretical. The lower values were less predictable. Pure oxygen-based values agreed more closely in the lower concentrations than did the air-based values, because the influence of the 0.03 per cent CO<sub>2</sub> in air lowered deflection by decreasing the absolute con-

centration changes of carbon dioxide presented to the instrument. Lack of completely theoretical response with oxygen base at low concentrations may have been due to either inaccuracy of record interpretation or slight errors in Haldane analysis, rather than the apparent sensitivity variation of the analyzer.

In practice during subsequent work, the instrument has been standardized frequently and calibration curves have been run in conjunction with the metabolic experiments. The factor governing accuracy of the method is the constancy of air flow rates in the main and aliquot circuits. Sensitivity of the gas analyzer is well within the limits desired for metabolic work. The instrument is sensitive to 0.01 per cent  $\text{CO}_2$ . Results are reproducible within the readability of the recording chart, i.e., one microvolt. The fact that the method depends solely upon carbon dioxide content rather than carbon dioxide and oxygen requires the assumption of a caloric equivalent of carbon dioxide. This caloric equivalent varies with the R.Q. At an R.Q. of 0.80 it is 3.04, at 0.85 it is 2.95 Cal./gram (6). Benedict (7) recommends 3.00 Cal./gram as the  $\text{CO}_2$  equivalent for a 24-hour period. The R.Q. values subsequently obtained on our subjects were quite variable but fell within a range which justified the use of 3.0 Cal./gram as the carbon dioxide equivalent.

## RESULTS

After calibration and standardization of the apparatus and recording instruments, application of the technique to measurement of energy expenditure was undertaken on 3 laboratory subjects. The subjects wore an A-13 oxygen demand mask, held in place by a 'Juliet type' harness. This type of mask was chosen for its adaptability to field conditions (fig. 4). To the mask was attached a hose leading to the analyzer assembly. Through mask and hose, air was drawn at a rate of 102 liters per minute. An analyzer aliquot was drawn by the pumping system previously described. The 3 subjects were used to adapt apparatus and technique to human energy study primarily with field application in mind. A series of treadmill exercises was obtained on each subject. The severity and duration of each phase of the exercise were made strictly uniform between subjects. From these data the energy expenditure of the 3 men for each phase of the activity was compared. A representative curve from one subject (no. 3) is given in figure 5. Deflection in microvolts on the tracing represents carbon dioxide output during rest, level walking ( $2\frac{1}{2}$  and 5 m.p.h.), a recovery period, additional rest, grade walking (10%,  $2\frac{1}{2}$  and  $3\frac{1}{2}$  m.p.h.) and recovery. The type curve was typical of all, although actual quantity output of carbon dioxide depended upon the individual. Equilibration of microvolt deflection to percentage

carbon dioxide for any point on the curve was obtained from standard values. One gram of carbon dioxide is equivalent to 3 Calories (6). By calculation, microvolt deflection could be read as calories per minute. To compare subjects, values must be made uniform by consideration of surface area. Figure



Fig. 4 A-13 OXYGEN DEMAND mask in use during field trials

6 graphically compares the average caloric expenditure for each subject during each phase of the test exercise. The data are given as Calories per square meter body surface per minute. The value given in the figure as 'rest' was evaluated by Haldane analysis in order to compare the infra-red method with a standard laboratory procedure. Comparison of two infra-red analyses on the subject is also made. The data are given in table 3

True basal rates for men of the age group are approximately 45 Cal./M<sup>2</sup>/hr.; therefore, the rest period should be considered pre-exercise.

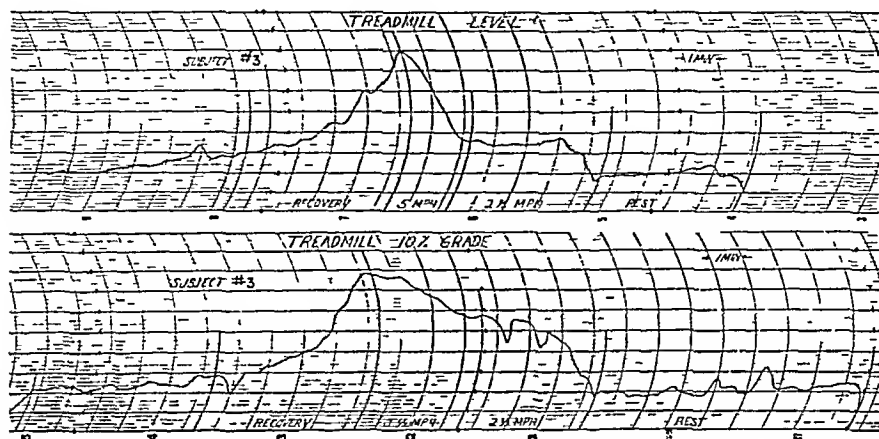


Fig. 5. ESTERLINE-ANGUS MILLIAMMETER recording of a subject exercising on the treadmill.

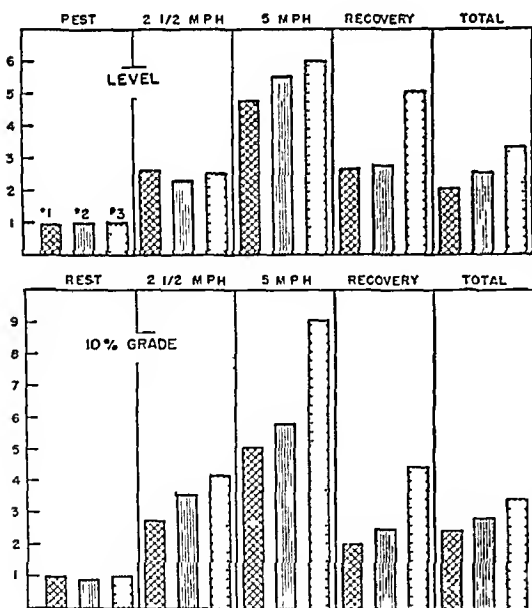


Fig. 6. COMPARISON OF THE ENERGY EXPENDITURE of 3 subjects. Treadmill activity. Values in Cal/M<sup>2</sup>/min.

The infra-red gas analyzer assembly was given a full field trial. Energy expenditure studies were made on soldier subjects undergoing prescribed mountain warfare training. The series included not only a comparison of the new technique with the standard field method of Douglas bag Haldane analysis over terrain on which the latter could be applied (1), but also the adaptation of the new technique to study of soldiers undergoing maneuvers the energy requirements of which had not been previously assessed. Technically,

the studied climbs were: a) mountain walk, a climb over a marked trail upon which both new and old analysis techniques were practiced; b)

scramble, a difficult climb over loose shale rock; *c*) belay, free climb up a perpendicular rock face utilizing hand and foot holds; and *d*) tension, or mechanically assisted climbing up an overhanging rock face. In addition to these data, direct comparisons have been made between different men undertaking identical activities, and also an assessment has been made of the influence of both confidence and experience on energy expenditure during mountain climbing. Two subjects from each of six companies were used. The subjects were average troops 18 to 19 years of age, 68 to 71 inches in height and 138 to 194 pounds in weight.

The metabolism study was coordinated with the mountain-training teaching schedule so that those men chosen were not deprived of their training. Each subject reported for energy expenditure studies according to a set schedule and was tested three times during a one-month training period, i.e., the first week, second week and third week. The severity of the assigned climb was governed by the subject's instruction in climbing technique. Early tests were simple mountain walking. Later tests were precision climbing, i.e., scramble, belay and tension. Some of the more difficult

TABLE 3. CALORIC EXPENDITURE AT REST, HALDANE AND INFRA-RED ANALYSIS

SUBJECT NO.	SURFACE AREA, M <sup>2</sup>	Haldane	CAL./M <sup>2</sup> /HR.	
			Infra-red	
1	1.77	57.5	55.2	58.4
3	2.02	58.5	60.2	61.2
2	1.90	59.0	58.3	54.4

phases of the study were made only on those members of the group who were considered by their military training instructors to be proficient. This policy minimized accidents.

*Comparison between Haldane and Infra-red Analyses.* A relatively rugged mountain walk was chosen as a standard effort for the subjects in order to compare the caloric expenditure values obtained by both the Haldane and the infra-red techniques. This course consisted of a 200-foot uphill path, the average grade of which approximated 58 per cent. Douglas bag samples were taken at rest, during ascent, while recovering after ascent and during descent of the standard grade. Over the same course, at a different time, an infra-red analysis was made. The energy expenditure for each phase of the standard exertion for each subject is given in table 4. Values obtained with the two methods were in closest agreement at resting levels. Increased exertion gave energy outputs which were comparable in trend and average only. The discrepancy between the two methods may be explained as due to individual variation in energy expenditure by a subject upon repetition of the same effort. A second set of Haldane analyses on one subject (I-078) over the same course illustrates this point (table 4). Comparable figures obtained by Lusk (8) are basal 0.86,

running 5.24, gymnastics 2.53 and football 7.32 Calories per square meter body surface per minute.

*Comparison of Infra-red Analysis Curves Between Subjects.* The analysis curves for output of CO<sub>2</sub> demonstrated rather close contour agreement between subjects when taken as initial exposure to a particular type of exercise. In figure 7 the analyzer curves, obtained from paired subjects undergoing three types of climbing training, are compared. They represent: a) paired subjects undertaking quick time (120 steps per min.) and double time (180 steps per min.) marching; b) climbing the 200-foot mountain walk previously described; and c) ascent and descent of a 400-foot course of mountain walk and shale scramble. The curves have been super-

TABLE 4. ENERGY EXPENDITURE, CAL/M<sup>2</sup>/MIN

SUBJECT	AREA, SQ. M.	REST-BEFORE EXERCISE		ASCENT 200 FT.		RECOVERY-POST ASCENT		DESCENT 200 FT.	
		Haldane	Infra-red	Haldane	Infra-red	Haldane	Infra-red	Haldane	Infra-red
L-032	2.08	.891	.802	4.86	5.21	1.27	2.58	2.20	3.78
L-110	1.96	.832	.796	4.26	4.35	2.12	2.61	2.39	3.28
H-025	1.76	.768	1.191	4.23	3.64	1.97	2.47	2.12	2.03
H-063	1.86	.761	.791	2.39	3.06	1.60	2.23	1.66	3.03
K-103	1.85	1.000	1.230	4.38	4.07	1.92	1.99	2.78	2.45
K-092	1.84	.952	.858	4.04	3.92	1.86	1.38	2.99	2.24
M-105	1.94	.944	1.000	4.35	2.94	1.53	2.48	3.12	2.37
M-114	1.91	.734	.644	3.48	4.02	1.29	2.04	1.94	2.65
S-046	1.88	.632	.665	4.89	4.33	1.70	1.98	2.49	2.59
S-051	1.92	.876	.906	3.74	3.34	1.37	2.08	2.73	2.43
I-080	1.81	1.022	.813	4.86	2.94	1.82	1.60	2.84	2.36
I-078	1.81	1.022	.951	3.62	3.48	1.41	1.63	2.79	2.40
I-078 (repeat)	1.81	.768		3.13		1.70		2.83	

imposed. The elapsed times differ slightly. On both of the climbs between ascent and descent there was a five-minute 'break' or recovery period.

The 400-foot course was a continuation of the 200-foot standard grade, and consisted of an additional 200 feet of very difficult shale rock scramble. The grade was somewhat steeper than that of the previous effort. The carbon dioxide output, converted to Cal./M<sup>2</sup>/min. for the total course showed fairly good agreement between men (table 5).

*Terrain Familiarity (Confidence) in Belay Climb.* In the laboratory, repetition of the same exercise by a subject did not give identical energy distribution, for he was apparently able to govern his energy expenditure in accordance with anticipated need. In the field, familiarity with terrain gave the man added confidence, which enabled him to perform an assignment in shorter time, at the same rate of caloric expenditure. In practice all comparisons have been made when the subjects had the same familiarity



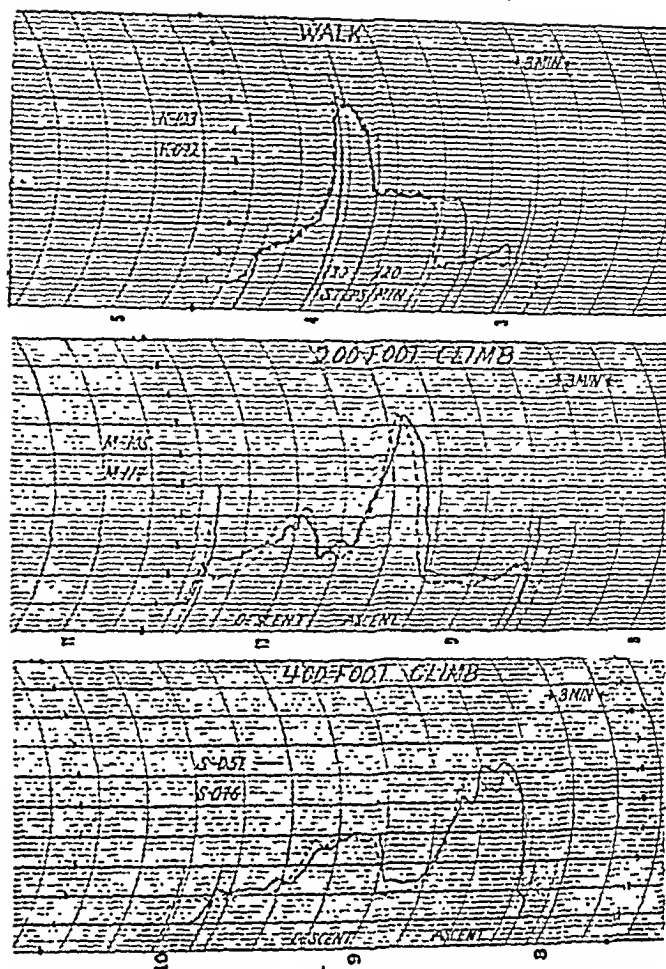


Fig. 7. COMPARISON OF ANALYTICAL CURVES obtained from paired subjects during field trials.

TABLE 5. FREE CLIMB AND SCRAMBLE—400 FEET AND RETURN

SUBJECT	TOTAL CAL.	TIME MIN.	CAL/MIN.	CAL/M <sup>2</sup> /MIN.
L-032	90.1	16.0	5.64	2.71
L-110	111.2	20.2	5.54	2.82
H-025	108.7	23.3	4.66	2.65
H-063	99.1	21.8	4.54	2.44
K-103	92.4	25.4	3.63	1.96
K-092	111.5	31.0	3.59	1.95
M-105	87.5	22.3	3.93	2.02
M-114	87.4	22.9	3.82	2.00
S-046	82.1	23.2	3.54	1.88
S-051	84.4	22.7	3.72	1.93
I-078	107.7	24.8	4.34	2.40
I-080	77.8	19.5	3.99	2.20

with a given terrain. Ideally, initial effort would have been preferable. To illustrate this point, we chose a difficult, totally unfamiliar climb and called for volunteers. Five of the 12 subjects agreed to undergo the test. Because of the hazard, the men were protected by a belaying line. This was a safety 'check fall' rope from the man's body to an assistant above him in

climb. No actual climbing aid was given by this rope, but its presence prevented serious falls. Each of the 5 volunteers made the climb (125 feet of perpendicular ascent) using only natural hand and foot holds. For all,

TABLE 6. BELAY CLIMB—CALORIC EXPENDITURE

SUBJECT	SURFACE AREA	TOTAL CAL.	TIME (MIN.)	CAL./M <sup>2</sup> /MIN.
K-103	1.85	106.1	21.0	2.72
K-092	1.84	74.6	14.6	2.74
H-029	1.80	101.5	18.0	3.14
H-025	1.76	84.0	15.0	3.18
I-080	1.81	104.5	17.3	3.36

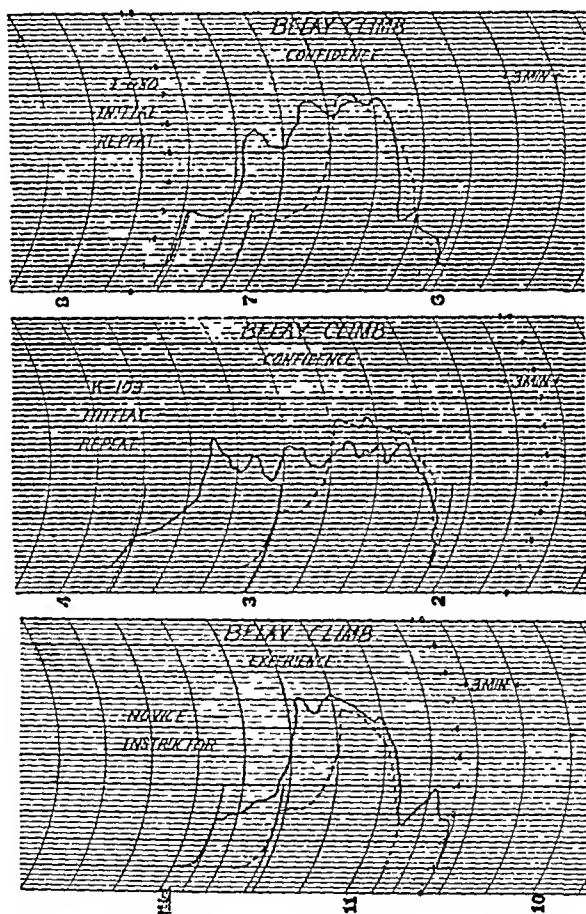


Fig. 8. RECORDS SHOWING THE INFLUENCE of confidence and experience on subjects undertaking the 'belay' climb.

it was avowed to be an initial attempt. Caloric expenditure and time requirements for the men are given in table 6.

On the second attempt at the same belay climb, required time was cut

by one-third without proportionate rise in energy expenditure. This improvement was the result of confidence. The rôle of experience was checked on 2 men from outside of the test group. One of these was a mountain-climbing instructor, and the other a presumably inexperienced 'jeep' driver. Each volunteered to make the climb. The instructor attacked the climb immediately, made no false starts and completed the course in less than two thirds of the time required by the novice. The trained man's caloric expenditure was less than that of the untrained. In figure 8 are records illustrating the influence of confidence and of experience.

*Climbing under Mental Tension.* The most difficult climb in mountain training is the 'tension' climb, so named because the subject was under stress while climbing. There were no hand holds or foot holds; the climber ascended by driving steel pegs into clefts in the cliff face, and drew himself up from peg to peg by means of a sling rope. This climb was forbidden to the soldier subjects because of the danger, but the instructor who cooperated on the belay climb agreed to a demonstration. His energy expenditure was relatively low and ascent very slow. During 10 feet of climbing which required 15 minutes, the caloric expenditure was 2.84 Cal./M<sup>2</sup>/min.

#### SUMMARY

A new technique for measurement of caloric expenditure during continuous activity has been developed. The Leeds and Northrup infra-red gas analyzer sensitized for carbon dioxide detection and equipped with an adequate pumping system for controlled air flow has been adapted to metabolic work and found satisfactory both in the laboratory and in the field. The A-13 oxygen demand mask in conjunction with long air lines carried by cable and pulley rigging offered a light-weight, comfortable, nonrestraining respirator for field study of energy expenditure. The new method offers instantaneous analysis and continuous records over protracted periods of exercise. These criteria have not been met by previous methods.

Caloric expenditure studies on men undergoing mountain warfare training have been accomplished. Comparative data of subjects undertaking prescribed activity in the laboratory and in the field are reported.

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## *Human Heat Production in Relation to Body Weight and Body Surface. I. Inapplicability of the Surface Law on Lean Men of the Tropical Zone*

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IN PREVIOUS PAPERS (1, 2) we have shown that the heat production of dogs in the city of São Paulo, Brazil, under the Tropic of Capricorn is more proportional to the body weight (proportional to  $W^{0.90}$ , which we suppose to express the metabolically active weight) than to the body surface. The surface law was, therefore, verified not to be valid for dogs of the tropical zone.

The investigations have now been extended to normal men living in the same city. In the present paper are reported the results obtained with lean men, that is, human beings poor in metabolically inactive fat tissue. The results show that the surface law is also not applicable to human beings living in the tropics.

On the other hand, by calculating the data obtained by the Nutrition Laboratory of the Carnegie Institution of Washington and by Boothby and Sandiford with lean men of cold climates, we found that their heat production is proportional to the weight at a power representing closely the skin area.

On discussing the subject we are led to admit that the difference between the American results and ours is due to the different climatic conditions and that the surface law, in being applicable only in colder climates, has a causal significance. All of the statistical analysis of the data in this paper was done by Dr. A. C. de Andrade, of this Institute, to whom we are deeply indebted.

*Experimental Subjects.* White Brazilian lean men, aged between 20 and 43 years, whose weight ranged between 49 and 81 kilograms, and who had been living in the city of São Paulo for at least several years, were studied. These men (of Brazilian or European descent) were all normally active but did not engage in athletics or severe muscular work. Clinical examination showed that they were in good health. Those individuals were considered as 'lean' whose weight in kilograms did not exceed the number of centimeters of height above one meter, this number being subject to a reduction of 10 per cent.

*Climatic.* The city of São Paulo lies exactly on the Tropic of Capricorn ( $23^{\circ}35' S$  and  $44^{\circ}38' W$  Greenwich) at an altitude of ca. 760 meters above sea level. The mean annual temperature is around  $18^{\circ}$  and the average relative humidity near 80 per cent. Barometric pressure averages ca. 695 mm. Hg. The determinations of heat production were made in all seasons of the year.

*Determination of the Minimal Heat Production (open circuit method).* On the day before the determination the subjects dined moderately, excluding from their meal meat, fish, milk, eggs and coffee. Nothing was eaten after 8:00 p.m. On the next morning they came to the laboratory without eating and went to a comfortable bed in an insulated and quiet room, the temperature of which was maintained between  $20$  and  $24^{\circ}C$ . They kept themselves in complete rest and muscular relaxation for half an hour, covered or uncovered, as they wished. A half mask, with inflated rubber edges, was tightly fitted on the patient's face and connected with Chauveau-Tissot valves. The inspired air was outdoors air; the expired air could both be expelled into the room or collected, in a compensated and controlled Tissot spirometer. The mask adjustment and the connections were always carefully controlled in order to avoid any leakage, even when the expiration tube was closed as a check some time before and after the determination. Five or ten minutes time was allowed for the subjects to become accustomed to the mask. During this period the dead space of the whole apparatus was washed with the expired air. The experiment was started by the collection of the air expired during exactly six minutes, in the Tissot spirometer. The volume of the expired air was then read and the temperature and the barometric pressure were recorded. A sample of the air was then collected for analysis. In each case a second collection of the expired air was made a little later, and a second sample taken for a second determination of heat production.

Owing to the fact that the patients were previously instructed, they never showed any uneasiness and kept themselves, during the whole procedure (about one hour), in what we considered to be a perfect repose. Another verification that no leakage existed was always made at the end of the second determination. The patients never complained of any ill-feeling or respiratory difficulty. In order to avoid any undetected systematic error, that might have influenced the results, two sets of instruments (i.e.: masks, valves and spirometers) were indifferently used during the course of the experiments.

The two air samples, from each patient, were analysed in two Haldane air-analysis apparatus which were calibrated by means of numerous analyses of atmospheric air during the course of the research. The maximum error

TABLE 1. MINIMUM HEAT PRODUCTION OF 50 LEAN ADULT MEN OF SÃO PAULO

SUBJECT	AGE	WEIGHT	HEIGHT	SKIN SURFACE	TOT. CAL./HR.	CAL./KG./HR.	CAL./SQ. M./HR.	OCCUPATION
	YRS.	KG.	M.	SQ. M.				
1 A. C. A.....	27	49.2	1.67	1.54	57.07	1.16	37.06	Phytopathologist
2 N. L.....	30	51.1	1.58	1.50	51.91	1.02	34.60	Medical student
3 A. G.....	26	51.3	1.62	1.53	55.24	1.08	36.11	Laboratory assistant
4 C. A. S.....	27	51.3	1.67	1.57	53.89	1.05	34.33	Physician
5 V. A.....	30	51.4	1.68	1.57	50.00	0.97	31.84	Laboratory assistant
6 L. G. S.....	20	53.0	1.74	1.64	56.50	1.07	34.45	Medical student
7 C. T. O.....	43	53.4	1.66	1.59	55.51	1.04	34.91	Bank clerk
8 D. B.....	40	54.0	1.62	1.57	50.30	0.93	31.85	Entomologist
9 A. O. N.....	33	54.0	1.68	1.62	55.57	1.03	34.30	Library assistant
10 G. F. C.....	33	54.2	1.70	1.63	56.91	1.05	34.91	Laboratory assistant
11 N. P.....	36	55.0	1.70	1.64	54.89	1.00	33.48	Physician
12 R. P.....	26	55.3	1.64	1.61	61.64	1.11	38.28	Laboratory assistant
13 J. V.....	25	55.4	1.77	1.69	57.00	1.03	33.73	Medical student
14 D. P.....	28	57.1	1.69	1.66	53.22	0.93	32.06	Biologist
15 A. M. F.....	24	57.9	1.81	1.75	63.18	1.09	36.11	Physician
16 F. L. C. R....	21	58.4	1.79	1.74	57.01	0.97	32.76	Medical student
17 F. M. R.....	37	58.4	1.70	1.67	64.59	1.10	38.68	Clerk
18 A. S.....	32	59.0	1.83	1.77	70.26	1.19	39.70	Rabbit breeder
19 S. D.....	22	60.0	1.75	1.74	65.52	1.09	37.65	Medical student
20 B. M. M.....	43	60.2	1.79	1.77	61.01	1.01	34.47	Laboratory assistant
21 V. L. S.....	23	60.3	1.75	1.74	62.12	1.03	35.76	Medical student
22 B. L. R.....	34	60.3	1.68	1.69	61.55	1.02	36.42	Laboratory assistant
23 G. A. A.....	24	61.2	1.78	1.77	71.93	1.18	40.63	Medical student
24 M. D.....	26	62.4	1.75	1.76	60.92	0.97	34.61	Laboratory assistant
25 J. B. P.....	22	62.4	1.78	1.78	67.08	1.08	37.62	Medical student
26 J. F. S.....	40	63.0	1.77	1.78	67.17	1.07	37.73	Laboratory assistant
27 D. F.....	31	63.0	1.71	1.74	59.91	0.95	34.43	Laboratory assistant
28 A. L. A.....	29	63.4	1.79	1.77	67.88	1.07	38.35	Clerk
29 A. A. S. B....	20	63.8	1.84	1.84	61.60	0.96	33.48	Medical student
30 D. S.....	30	63.8	1.75	1.78	60.26	0.95	33.85	Medical student
31 R. L. A.....	32	64.0	1.76	1.78	56.50	0.88	31.74	Entomologist
32 J. P.....	28	64.5	1.79	1.82	69.94	1.08	38.43	Library assistant
33 O. M. M.....	35	65.0	1.84	1.86	69.50	1.07	37.26	Medical student
34 O. C.....	34	65.0	1.78	1.82	68.34	1.05	37.55	Laboratory assistant
35 M. A. R.....	21	66.0	1.82	1.85	65.89	1.00	35.62	Medical student
36 J. S. P.....	24	66.8	1.78	1.84	72.00	1.08	39.12	Medical student
37 D. C.....	24	67.0	1.79	1.84	62.78	0.94	34.12	Radio technician
38 I. S.....	24	68.0	1.83	1.88	68.10	1.00	36.22	Medical student
39 O. R.....	30	68.2	1.85	1.90	68.03	1.00	35.80	Physician
40 O. P.....	25	68.8	1.80	1.87	69.95	1.02	37.41	Clerk
41 C. C.....	25	69.0	1.80	1.87	75.78	1.10	40.52	Painter
42 W. A. M.....	28	69.1	1.77	1.83	67.22	0.97	36.34	Laboratory assistant
43 A. J. S.....	36	69.2	1.86	1.92	71.52	1.03	37.25	Driver
44 G. S. S.....	23	71.5	1.86	1.94	65.91	0.92	33.97	Business man
45 E. T.....	29	72.0	1.82	1.92	71.39	0.99	37.18	Laboratory assistant
46 M. T. A.....	21	73.0	1.85	1.95	70.36	0.96	36.08	Medical student
47 W. C.....	24	73.8	1.84	1.96	76.99	1.04	39.28	Glassworker
48 W. P.....	29	75.6	1.85	1.98	68.81	0.91	34.75	Medical student
49 A. S.....	23	78.0	1.92	2.06	90.12	1.16	43.75	Engineering student
50 P. S.....	35	81.0	1.90	2.08	71.44	0.88	34.34	Singer

of the combined percentage of  $O_2$  and  $CO_2$  did not exceed, in our determinations, 0.03 per cent of the theoretic percentage. The total calories were calculated from the  $O_2$  consumption, using the calorific value of 4.8. The skin areas were determined by the Du Bois' chart, the weight and the height of the naked patients having been measured immediately after the determination. In all, 54 patients were studied; 4 of these were rejected one for showing a very low heat production and the others for having shown great discrepancy between the two determinations. The average difference between the two determinations in each of the 50 individuals here presented was 3.4 per cent.

TABLE 2. MEAN MINIMUM HEAT PRODUCTION OF 50 LEAN ADULT MEN OF SÃO PAULO AND OF LEAN ADULT AMERICAN MEN

WEIGHT RANGE	NUMBER OF CASES	CAL./KG./HR.	CAL./SQ. M./HR.
<i>Men of São Paulo</i>			
Kg.			
49-55	10	1.04	34.43
55-60	8	1.05	35.60
60-65	14	1.02	36.08
65-70	11	1.02	37.08
70-81	7	0.98	37.05
<i>American Men (5, 6, 7)</i>			
49-55	16	1.16	38.56
55-60	24	1.12	38.12
60-65	33	1.09	38.69
65-70	15	1.06	38.47
70-75	5	1.04	38.84

## RESULTS

Table 1 shows the results obtained with 50 lean men, the lowest determination only in each patient being taken into consideration. When the individuals are grouped according to their weight (Table 2) it becomes evident that the minimum heat production per square meter increases from group to group as the weight increases.

*Statistical Treatment of the Data.* The exponent of the weight in the equation  $C = aW^b$  was calculated by the method of least squares, using the logarithms of the number of total calories per hour and of the weight in kilograms so that  $\log C = \log a + b \log W$ . The exponent  $b$  in the first equation is the coefficient of regression in the second one. The equation for the data of the 50 subjects in table 1 is  $\log C = 0.3091 + 0.8331 \log W$  with an error of estimate of  $\pm 0.03131$ . This corresponds to the equation  $C =$

$2.038 W^{0.83}$  with a standard error of  $+7.5$  per cent and  $-7.0$  per cent. The standard error of the coefficient of regression,  $b$ , is  $\pm 0.0851$ .

In figure 1, where these results are represented, A A' is the regression line of our data and the two parallel lines, corresponding to the 99 per cent confidence level, based on the errors of estimate, is also shown.

On the other hand, when the equation is calculated using the number of total calories per hour and the body surface in square meters, as obtained from the Du Bois' chart (S), it is found that:  $C = 30.02 S^{1.32}$  with a percentage standard error of  $+6.3$  and  $-5.9$  per cent. The standard error of

Fig. 1. TOTAL MINIMUM HEAT PRODUCTION of 50 lean adult men of São Paulo plotted against their weights on a logarithmic scale.

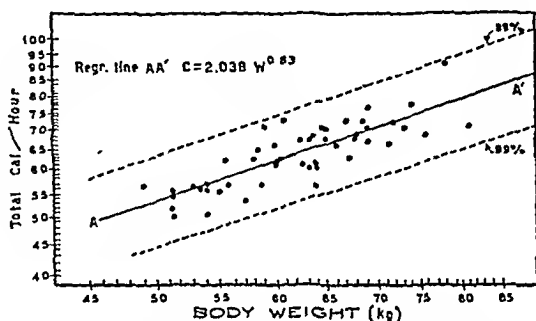
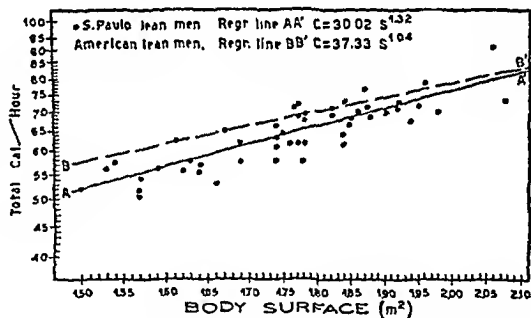


Fig. 2. TOTAL MINIMUM HEAT PRODUCTION of lean men of São Paulo plotted against their body surfaces on a logarithmic scale. The regression line for the data on American lean men is also traced.



the coefficient of regression is  $\pm 0.1121$ . In figure 2 the heat production of our patients is plotted against their body surface and the respective regression line is traced.

#### DISCUSSION

We shall discuss separately our own results, results obtained in the United States and the discrepancies between these results.

The results reported in this paper show that the heat production of Brazilian lean men, inhabitants of São Paulo, is not proportional to body surface (table 2), the Rubner-Richet surface law not being applicable. This is confirmed by the fact that the  $t$ -test reveals a highly significant difference between the calculated power of the surface (1.32) and 1.00, which would



be the power of  $S$  if the heat production was strictly proportional to the body surface.

In relation to the body weight the equation found is:  $C = 2.038 W^{0.83}$ .

A significant difference (95 per cent confidence level) exists between 0.83 and 1.00, which signifies that the heat production cannot be considered as strictly proportional to the body weight.

The data now obtained confirm those previously reported for dogs (2) for which the equation was:  $C = 2.000 W^{0.90}$ .

We can suppose that  $W^{0.83}$  expresses the metabolically active weight of lean men, while  $W^{0.90}$  expresses that of the dog. No significant difference (55 per cent probability) was found between the 0.83 and the 0.90 powers. However this difference could point to a smaller percentage of metabolically active tissue in man as compared with dog. In this connection, the close agreement between the values 2.038 and 2.000, which expresses the heat production by the unity of metabolically active weight of the lean man and dog, respectively, is remarkable. Much the same is being verified with well proportioned men (3).

In order to calculate the basal metabolism according to our data in our warm climate the minimum metabolism should not be related to body surface but to body weight at a power ( $W^b$ ), which would represent the metabolically active weight.

According to the above equation, we propose to express the basal metabolism of lean, white, Brazilian males, between 20 and 43 years old, living under the Tropic of Capricorn, by the expression

$$\text{Basal metabolism} = \frac{\text{Cal. p. h.}}{W^{0.83}} \approx 2.038 \text{ Cal.}$$

The value 2.038 is therefore the standard that should be employed for mean under the above conditions. The statistical treatment has shown that in 99 per cent of the cases the variation of this value lies between  $+20.0$  and  $-17.0$  per cent, that is about  $\pm 18.5$  per cent. In 90 per cent of the cases the variation lies between  $+12.6$  and  $-11.2$  per cent, that is about  $\pm 12.0$  per cent.

The weight in kilograms of the subjects here presented has a value corresponding to the number of centimeters of their height about one meter, this number being reduced by 10 to 28.9 per cent. Within this range of reduction when the total heat was plotted against the weight (in logarithmic scale) no particular distribution according to the reduction was apparent. This can be attributed to the fact that the lower weights in relation to height are due to the poverty in metabolically active tissue rather than to poverty

in fat depots and suggests that the relative amount of fat is quite comparable among these lean individuals. On the contrary, the level of heat production is quite different when we consider individuals in which the weight in kg. exceed the number of centimeters of height above one meter minus 10 per cent, as will be shown in another paper by a covariance analysis (3).

We have previously stated that it would be desirable to confirm by a greater number of experiments the 0.6 power of the weight calculated by Brody (4) for the combined experiments of several authors, which is significantly different from the 0.90 power we have found for dogs under tropical conditions. As those authors worked in Europe and North America, we pointed out, that, if confirmed, the 0.6 power could well correspond to the surface law on dogs in cold climates. We would then come to the conclusion that the surface law is not a mere coincidence but a thermal causal law (2).

For human beings, however, the matter may be examined by means of the data from the Nutrition Laboratory of the Carnegie Institution of Washington, published in detail by Harris and Benedict (5) and by Benedict (6). In these two well known and fundamental series (the first of which was largely used in the establishment of the classical standards of Benedict, Aub and Du Bois, Dreyer, and of Carpenter) we found a total of 82 individuals comparable to our lean men under the same conditions; viz.: sex, alimentation, age, height-weight ratio and occupation, but living in colder climates.<sup>1</sup> To this we could add the 14 normal persons that, under similar conditions, were investigated by Boothby and Sandiford (7) in the only series which as far as we know, was published in detail.<sup>2</sup> From the data on these 96 individuals we calculated by the method of least squares the following equation:  $\log C = 0.5863 + 0.6929 \log W$  with an error of estimate of  $\pm 0.03149$ . This corresponds to the equation:  $C = 3.858 W^{0.69}$  with a percentage standard error of  $+7.5$  and  $-7.0$  per cent.

The error of the coefficient of regression is estimated as  $\pm 0.0664$ .

If we suppose that the surface law is valid in cold climates,  $W^{0.6929}$  must be expected to represent the skin area. We checked this by calculating, for 96 American lean subjects, the surface from 0.1  $W^{0.6929}$  (0.1 being used to obtain directly square meters, starting from weight in kilograms) and comparing it with the cutaneous area, measured in the same subjects by the Du Bois' chart. We found that the mean of the Du Bois' surface was only 0.88 per cent greater than that calculated from the weight at the 0.6929 power, the two maximum deviations being  $+6.8$  per cent and  $-3.7$  per

<sup>1</sup> These men are, in the first series (5) the subject number (table C): 37, 41, 45-48, 51-53, 55, 57-66, 68-72, 74-76, 78, 82-86, 88-89, 93, 95-102, 104-110, 112-117, 122-123, 126-133, 135-136. In the second series (6) subject numbers (table 1): 149, 150, 153, 154, 156-163.

<sup>2</sup> These are in their table 3: 63, 66-69, 73-74, 77, 79, 81-82, 87, 89, 93.

cent. The fact is impressive that the skin area so accurately determined by Du Bois from an empirical equation ( $W^{0.425} \times H^{0.725} \times 71.84$ ) is, in the case of lean men, so close to values calculated from  $W^{0.6929}$ , which for purely theoretical reasons we consider as representative of the surface of the heat loss.

So, unlike what occurs with our subjects, the heat production of the American lean man is constant when referred to the Du Bois' body surface, independently of the weight range of the individuals. This is also shown in table 2, in which we ranged the American subjects according to their weights, as we have already done for our subjects.

That the surface law is valid for American lean men is again shown by calculating the equation using the total calories per hour and the body surface, determined by the Du Bois' chart. The following equation was found:  $C = 37.33 S^{1.01}$  with a percentage standard error of  $+7.5$  and  $-7.0$  per cent. The error of the coefficient of regression is estimated as  $\pm 0.1032$ . The power of  $S$  (1.04) is not statistically different from 1.00, which would express a strict proportionality of the heat production to the body surface.

An application of the 't' test shows that there is only one chance in 10 that from a population with a coefficient of regression of 0.69 (the power of the weight calculated for American men) a sample is drawn with a coefficient of 0.83, the power found for lean men of São Paulo. The chances are two in 10 that those two coefficients would be found in two samples from one population. Following the suggestion of Dunn (8) not to fix "an arbitrary standard of probability as an indication of significance" but rather to consider our "particular problem," we feel rather confident in stating that the difference found between the two powers of weight is significant.

This opinion is reinforced when we consider the heat production in relation to the body surface. The 't'-test of the difference between the powers of the surface of the American lean men (1.04) and that of the São Paulo lean men (1.32) shows that the odds are only 7 out of 100 that such a difference would occur in two samples from the same population. Graphically this is represented in figure 2, which shows the different slopes of the respective regression lines.

This difference between our results and those obtained in the United States would speak against the possibility of the heat production of American lean men being causally related to the metabolically active weight, the active mass of protoplasmic tissue, the weight of organs, the amount of blood, the cross section of the aorta or the cross section of the trachea as claimed by different authors who have considered the surface law to be a mere coincidence. As a matter of fact, if any of the above hypotheses were correct, our lean men would show a heat production also proportional to  $W^{0.69}$ , be-

cause there is no reason why those values should be different in Brazilian and American individuals.

In order to understand the fact that the heat production in São Paulo is proportional to  $W^{0.83}$  and in the U. S. to  $W^{0.69}$ , we offer the following explanation based on the theory proposed by A. Ozorio de Almeida (9). According to this theory the minimal metabolism would depend on the current metabolism of the subject (*metabolisme habituel*) and the surface area would have a lesser influence in warm climates than in cold ones. Our explanation is based on the fact that there exists a considerable difference in the environmental temperature in the American cities where the data were collected and the temperature in São Paulo. In this city the mean annual temperature is nearly  $18^{\circ}\text{C}$ ., the mean temperature of the coldest month being ca.  $15^{\circ}\text{C}$ . and that of the warmest month being ca.  $21^{\circ}\text{C}$ . In Boston, where the Nutrition Laboratory of the Carnegie Institution is located, the annual normal temperature is ca.  $10^{\circ}\text{C}$ ., the minimum normal monthly temperature ca.  $-2^{\circ}\text{C}$ ., the maximum  $22^{\circ}\text{C}$ . (11). We were not able to obtain the normal temperatures of Rochester, Minn., where Boothby and Sandiford worked, but in Minneapolis, Minn., a neighboring city, the figures are: annual normal temperature ca.  $7^{\circ}\text{C}$ ., minimum normal monthly temperature ca.  $-11^{\circ}\text{C}$ . and the maximum ca.  $22^{\circ}\text{C}$ . (11).

Thus, in these American cities where there prevails a much greater difference of temperature between the body surface and the milieu than in São Paulo, the rate of heat loss is also greater. We suppose, that in those colder climates the heat loss may be the dominant factor in determining the heat production and in this case the heat production adjusted to the heat loss shows itself proportional to the surface. This is an explanation of the applicability of the surface law in colder climates. In warmer climates, as for instance in São Paulo, the rate of heat loss, being more frequently smaller, becomes insufficient to condition the heat production. The heat production then becomes proportional to the metabolically active weight and is independent of the heat loss through the body surface, the Rubner-Richet law not being applicable in such cases.

The fact that the surface law is applicable in cold and not in warm climates leads us to the general conclusion that it is a causal thermal law and not a coincidence.

#### SUMMARY AND CONCLUSIONS

In a previous paper we have shown that the heat production of dogs, living in the city of São Paulo, Brazil, is proportional to  $W^{0.90}$  and not to the body surface. The results of similar investigations on men are reported in the present paper.

The minimum heat production (by the open circuit method) of fifty Brazilian healthy, lean men, of 20-43 years of age, weighing between 49 and 81 kilograms, not practicing muscular activities, and living in São Paulo (a city exactly under the Tropic of Capricorn), was determined.

The heat production was found to be proportional to  $W^{0.83}$ , which we interpreted as the metabolically active weight of lean men, and not related to the body surface. The equation found is  $C = 2.038 W^{0.83}$  which agrees with the equation previously found for tropical dogs.

By the analysis of the data, reported by American authors for lean men under similar conditions but living in cold climates, we found that their heat production was proportional to  $W^{0.69}$ . We verified that the weight at this power represents very closely the skin surface, measured by the Du Bois' chart.

The fact that the surface law is applicable in colder and not in warmer climates is interpreted as a demonstration that it is not a mere coincidence but a causal thermal law.

As in warmer climates the heat production is not proportional to the body surface we propose to express the basal metabolism in those climates by referring the total minimal calories per hour to the metabolic active weight. For lean men, under the above conditions, we propose the following equation:

$$\text{Basal metabolism} = \frac{\text{Cal. per hour}}{W^{0.83}} = 2.038$$

This standard has a maximal variation of ca.  $\pm 18.5$  per cent in 99 per cent of the cases, and of ca.  $\pm 12$  per cent in 90 per cent.

Thanks are due to Dr. C. A. Salvatore for clinical examination of the patients and to J. P. Forster and E. Pansardi for helping in the determinations.

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## *Human Heat Production in Relation to Body Weight and Body Surface. II. Inapplicability of the Surface Law on Well Proportioned Men of the Tropical Zone*

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AS A RESULT OF PREVIOUS INVESTIGATIONS we have found that the heat production of dogs in São Paulo (Brazil), just under the tropic of Capricorn, is not proportional to the body surface. It is proportional to the body weight at the power of 0.90, which we interpreted as the metabolically active weight of dogs (1,2). More recently, we experimented with lean men (men poor in the metabolically inactive fat tissue), which we considered comparable to mongrel dogs, from the point of view of fat content. We found that the heat production of the lean men in São Paulo, likewise, does not conform with the surface law but is proportional to  $W^{0.83}$ . By calculating the American data obtained on lean men in cold climates, we found a heat production proportional to  $W^{0.69}$ , which we verified to represent very closely the body surface of lean men (3).

The investigations were extended as reported herein to men presenting an average amount of fat tissue, who are here called *well proportioned* men. The results showed that the surface law is not applicable in the tropics, thus confirming the previous investigations carried on in São Paulo. Again, by calculating the American data obtained for well proportioned men, we found that for them the surface law is applicable in cold climates. The conclusion is drawn, as previously found, that the surface law is a causal, thermal law.

All the statistical treatment of data was done by Dr. A. C. Andrade, to whom we are deeply indebted.

### EXPERIMENTAL PART

The subjects employed were white Brazilian, well proportioned men, aged between 20 and 47 years, whose weight ranged between 51.6 and 90.4 kilograms and who had been living in the city of São Paulo for at least several years. These men were not engaged in heavy manual labor. Practically all were employed in sedentary occupations. A clinical examination showed that they were in good health.

We consider as well proportioned men individuals whose weight in re-

TABLE 1. MINIMUM HEAT PRODUCTION OF 50 WELL PROPORTIONED MEN OF SÃO PAULO

SUBJECT	AGE	WEIGHT	HEIGHT	SKIN SURFACE	TOT./ CAL./ HR.	CAL./ KG./ HR.	CAL./ SQ. M./ HR.	OCCUPATION
	yrs.	kg.	m.	sq. m.				
51 B. M. C.....	46	51.6	1.52	1.46	46.17	0.89	31.62	Physician
52 A. R.....	42	52.0	1.57	1.51	46.60	0.90	30.86	Laboratory asst.
53 G. S.....	41	53.0	1.57	1.53	51.30	0.97	33.53	Laboratory asst.
54 A. G.....	28	56.4	1.62	1.59	57.57	1.02	36.20	Laboratory asst.
55 A. T.....	29	57.4	1.62	1.61	55.85	0.97	34.69	Laboratory asst.
56 N. S.....	34	58.4	1.59	1.60	51.94	0.89	32.46	Library asst.
57 P. R. A.....	31	58.6	1.60	1.61	56.00	0.95	34.79	Biologist
58 D. B.....	43	59.3	1.62	1.63	55.24	0.93	33.89	Entomologist
59 G. C. N.....	27	59.6	1.62	1.63	54.78	0.92	33.60	Medical student
60 P. P. R.....	33	60.7	1.63	1.66	58.57	0.96	35.28	Business man
61 U. V. D.....	20	62.0	1.63	1.67	59.42	0.96	35.58	Medical student
62 E. E. T.....	33	62.8	1.61	1.67	59.47	0.95	35.61	Biologist
63 C. L. M.....	25	62.8	1.66	1.70	63.94	1.02	37.61	Medical student
64 W. R.....	42	63.3	1.68	1.73	50.83	0.80	29.83	Laboratory asst.
65 A. V. M.....	39	64.2	1.62	1.69	58.29	0.91	34.49	Clerk
66 M. D. A.....	36	64.4	1.62	1.72	57.78	0.90	33.60	Bacteriologist
67 A. A. B.....	45	65.0	1.71	1.77	60.64	0.93	34.26	Phytopathologist
68 J. F.....	43	65.6	1.71	1.77	63.76	0.97	36.02	Laboratory asst.
69 J. P. J.....	32	65.9	1.71	1.78	62.86	0.96	35.31	Physician
70 M. D.....	24	66.0	1.67	1.75	57.82	0.87	33.04	Medical student
71 D. F. G.....	28	66.2	1.70	1.77	66.67	1.01	37.67	Medical student
72 A. A.....	34	66.4	1.70	1.77	65.46	0.98	36.98	Laboratory asst.
73 J. M. G.....	42	66.6	1.64	1.74	56.28	0.84	32.34	Laboratory asst.
74 A. J. Q.....	39	68.0	1.72	1.81	66.77	0.98	36.89	Laboratory asst.
75 A. P. O.....	40	68.4	1.66	1.77	69.33	1.01	39.17	Laboratory asst.
76 J. T. M.....	47	68.5	1.71	1.80	69.18	1.01	38.43	Laboratory asst.
77 A. B.....	35	69.2	1.69	1.80	66.77	0.96	37.09	Laboratory asst.
78 E. T. M.....	41	70.6	1.75	1.85	61.44	0.87	38.21	Business man
79 P. R. R.....	26	71.4	1.69	1.82	61.96	0.88	34.59	Physician
80 E. N.....	39	72.0	1.77	1.87	64.24	0.89	34.35	Laboratory asst.
81 W. O. H.....	27	72.4	1.73	1.86	60.63	0.84	32.60	Biologist
82 M. C. L.....	40	73.6	1.75	1.88	61.27	0.83	32.59	Laboratory asst.
83 B. S.....	34	74.0	1.71	1.86	64.54	0.87	34.70	Clerk
84 J. L.....	32	76.0	1.82	1.97	72.80	0.96	36.96	Rabbit breeder
85 A. R.....	30	76.0	1.84	1.98	65.00	0.85	32.83	Mechanic
86 O. G.....	28	76.4	1.81	1.96	71.16	0.93	36.31	Biologist
87 S. R.....	33	76.8	1.81	1.97	68.51	0.89	34.78	Business man
88 M. R.....	42	76.9	1.78	1.95	66.92	0.87	34.32	Physician
89 J. E. S. R. J.....	25	77.4	1.84	2.01	65.42	0.84	32.55	Medical student
90 C. A. M.....	22	78.0	1.80	1.97	63.90	0.82	32.44	Medical student
91 A. N. F.....	37	78.0	1.78	1.95	69.73	0.89	35.76	Laboratory asst.
92 A. F. L.....	25	78.7	1.84	2.02	67.46	0.86	33.39	Medical student
93 A. M.....	33	79.0	1.86	2.03	66.43	0.84	32.72	Laboratory asst.
94 A. C. C. N.....	23	80.4	1.86	2.04	77.68	0.96	38.08	Medical student
95 O. D. S.....	32	81.4	1.85	2.04	68.50	0.84	33.59	Physician
96 C. F.....	35	82.0	1.80	2.01	68.41	0.84	34.03	Physician
97 M. A. M. J.....	45	82.0	1.83	2.03	71.00	0.86	34.97	Insp. of immigration
98 L. D.....	34	84.7	1.84	2.07	81.34	0.96	39.30	Physician
99 J. F. B.....	31	85.2	1.86	2.09	66.69	0.78	31.91	Medical student
100 B. S.....	39	90.4	1.93	2.21	79.57	0.88	36.00	Business man

lation to their height, ranges between the following limits. The minimum limit in kilograms is the number of centimeters in height above one meter, decreased by 9.9 per cent. The maximum limit in kilograms is the number of centimeters in height above one meter increased by 5 per cent.

*Climate.* The data on the climate of São Paulo have already been given (2, 3).

*Method for Determining the Minimal Heat Production.* The open circuit method employed was exactly the same as already described in detail (3). In all, we investigated 51 patients. One of these was rejected for

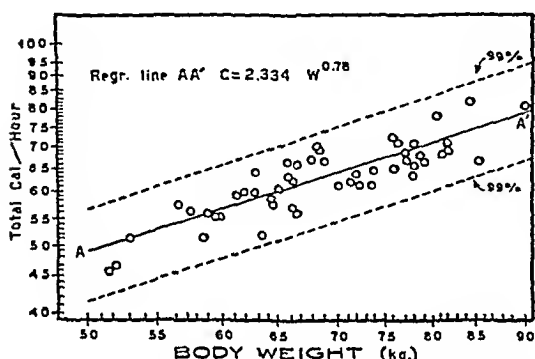


Fig. 1. TOTAL MINIMUM HEAT PRODUCTION of 50 well proportioned men of São Paulo, plotted against their weights on the logarithmic scale.

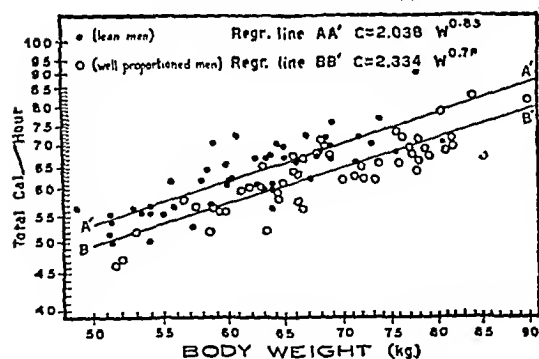


Fig. 2. TOTAL MINIMUM HEAT PRODUCTION of well proportioned and of lean men of São Paulo plotted against their weights on the logarithmic scale. The respective regression lines show the different levels of the heat production.

having a very low heat production with no agreement between the two successive determinations. The average difference between the two determinations made in each of the patients reported here was 3.9 per cent.

*Results.* Table 1 contains the data obtained with 50 well proportioned men in São Paulo. Only the lowest heat production value of each patient was taken into consideration.

*Statistical Treatment of Data.* The exponent of the weight in the equation  $C = aW^b$  was calculated by the method of least squares, using the logarithms of the number of total calories per hour ( $C$ ) and of the weight in



kilograms ( $W$ ), so that  $\log C = \log a + b \log W$ . The exponent  $b$  in the first equation is the coefficient of regression in the second one.

The equation for the 50 determinations in table 1 is  $\log C = 0.3681 + 0.7772 \log W$  with an error of estimate of  $\pm 0.02726$ . This corresponds to the equation  $C = 2.334 W^{0.78}$  with a percentage standard error of  $+6.5$  per cent and  $-6.1$  per cent. The standard error of the coefficient of regression is  $\pm 0.06614$ .

In figure 1, where these results are represented,  $AA'$  is the regression line of our data and the two parallel lines corresponding to the 99 per cent confidence level, based on the error of estimate, is also shown.

### DISCUSSION

In the first place we will compare the equation

$$C = 2.334 W^{0.78} \quad 1$$

which represents the heat production of well proportioned men in São Paulo in relation to the body weight, with the equation

$$C = 2.038 W^{0.83} \quad 2$$

we previously found to represent the heat production lean men of the same city in function of the weight (3).

A covariance analysis made of these two series of men (50 in each series) shows that the adjusted means of the heat production of the well proportioned men were lower than those of the lean men, with high statistical significance. On the other hand the covariance analysis did not reveal a significant difference between the coefficients of regression of the above equations.

These results are graphically shown in figure 2, where the 100 determinations are plotted and their corresponding regression lines are traced. It can be seen that each one of the series shows a different level of heat production.

In the case of lean men, we interpreted  $W^{0.83}$  as the metabolically active weight. The present investigation shows that the heat production in well proportioned men is a function of  $W^{0.78}$ . As a matter of fact, it is to be expected that the well proportioned men would have a metabolically active weight somewhat lower than that of the lean men of the same weight and that the difference between the powers of weight would be of the magnitude found. The fact that the statistical analysis has not revealed a significant difference between the two powers of weight, however, does not allow from the available data a proof or disproof of this interpretation.

Of course, as the two series have different levels of heat production, an equation expressing the heat production in function of the weight by pooling together lean and well proportioned men is to be considered meaningless. Such an equation for the 100 determinations is  $C = 3.905 W^{0.66}$ . This equation does not fit the data, for 39.05 cannot be taken as representing the heat production per square meter either of our lean mean as seen in table 1 of our previous paper (3) or of the well proportioned men (table 1). Consequently it is only a matter of pure coincidence that  $W^{0.66}$  (different both from  $W^{0.83}$  and  $W^{0.78}$ ) expresses the body surface. This coincidence may, however, explain why it has never before been suspected that the heat production in warm climates is not proportional to the body surface. In fact, the determinations of other investigators in warm climates have been carried out indifferently with lean, well proportioned and fat individuals.

In order to compare our data with those obtained in cold climates, we calculated the data obtained on well proportioned men, both by the Nutrition Laboratory of the Carnegie Institution of Washington (series I, published by Harris and Benedict, 4; and series II, by Benedict, 5<sup>1</sup>) and by Boothby and Sandiford 6<sup>2</sup> (the only series they published in detail to our knowledge).

From these sources, a total of 46 individuals under the same conditions as ours, but from cold climates, could be statistically treated. According to these data, the equation, expressing the relation of the minimal heat production to weight, was found to be  $C = 4.088 W^{0.67}$  with a percentage standard error of +8.4 per cent and -7.7 per cent. The standard error of the coefficient of regression is 0.1407. The maximal variations are  $\pm 21.0$  per cent in 99 per cent of the cases and  $\pm 13.4$  per cent in 90 per cent of the cases.

The weight in kilograms at the power of 0.67, to which the heat production is proportional (when multiplied by 0.1 to obtain square meters), expresses very well the body surface of these well proportioned men (with an average difference of -5.6 per cent of that calculated by the Du Bois' chart). This fact shows that the surface law holds good not only for the American lean men (3) but also for the American well proportioned men.

The above facts, confirming our previous reports on dogs and lean men, showing that the surface law is applicable in cold climates but not in warm climates (see climatic data in our previous paper), can be explained as before (2, 3) by the different rates of heat loss by the body surface in different

<sup>1</sup> These men are in the first series (4); the subjects number (table C): 29, 32-35, 39, 42-44, 49-50, 54, 56, 80, 92, 103, 119-121, 124-125, 134. In the second series (5) subjects number: 141-143, 145-148, 152.

<sup>2</sup> These men are in their table 3 (6): 62, 64-65, 70-72, 75, 78, 83-86, 90, 92, 94-95.

environmental temperatures. These findings reinforce our opinion that the surface law is really a thermal causal law.

As  $W^{0.78}$  does not express the body surface of the well proportioned men (actually it would correspond to a surface in the average 47.9 per cent greater than that of the body surface from the Du Bois' chart), the surface law cannot be applied to these men in warm climates. As a consequence, it is not reasonable to refer the heat production of these men to their body surface, as it is in cold climates.

It is our opinion that the basal metabolism in warm climates must be calculated by dividing the total heat production by  $W^b$ , which we suppose to represent the metabolically active weight.

Therefore, we propose for the well proportioned men of tropical climates the following standard, based on the results presented here:

$$\text{Basal metabolism} = \frac{\text{Calories per hour}}{W^{0.78}} = 2.334$$

with a maximal variation of  $\pm 16.2$  per cent in 99 per cent of the cases and  $\pm 10.3$  per cent in 90 per cent of the cases.

As can be deduced from the equations 1 and 2, the heat production per unit of metabolically active tissue of the well proportioned men (2.334) is about 15 per cent higher than that of the lean men (2.038). This fact can be explained on the lines already imagined by Benedict (7), by admitting that in the well proportioned men, the muscles, having to sustain and transport a greater amount of metabolically inactive tissue (chiefly fat), present a higher metabolism than that of lean men.

#### SUMMARY AND CONCLUSIONS

The minimal heat production of 50 well proportioned Brazilian men, in São Paulo, on the tropic of Capricorn, was investigated. All these men were adults and their weights ranged between 51.6 and 90.4 kilograms. They were not engaged in heavy manual labor and their ages ranged from 20 to 47 years. The equation found for the data obtained is  $C = 2.334 W^{0.78}$ .

It shows that the total calories per hour are proportional to the weight at a power that does not express the body surface, but which we believe to represent the metabolically active weight of the well proportioned men. These results confirm our previous conclusions on the subject with lean men and dogs in São Paulo.

By calculating the data of the literature on the heat production of the well proportioned American men, we found the equation  $C = 4.088 W^{0.67}$  which shows that for American individuals, the heat production is propor-

tional to  $W^{0.67}$ . The weight at this power nearly represents the body surface as calculated by the Du Bois' chart. We have already obtained the same results by studying the data on American lean men.

The fact that the surface law holds good in cold climates and not in warm ones is interpreted as signifying that this law has a thermal significance.

The basal metabolism in warm climates (contrary to what occurs in cold climates) cannot be calculated by relating the heat production to the body surface. Therefore, we propose (based on all the data we have as far obtained) that in the tropics the basal metabolism be calculated by dividing the hourly heat production by the metabolically active weight. For well proportioned men, in the conditions we investigated, the basal metabolism standard should be

$$\text{Basal metabolism} = \frac{\text{Calories per hour}}{W^{0.78}} = 2.334$$

with a maximal variation of  $\pm 16$  per cent in 99 per cent of the cases and of  $\pm 10$  per cent out of 99 per cent of the cases.

The somewhat higher heat production per unit of metabolically active weight of the well proportioned men, when compared to that of the lean men, is attributed to a higher metabolic activity of the muscles for supporting and transporting a greater mass of inactive tissue.

Thanks are due to Dr. C. A. Salvatore for the clinical examinations and to J. P. Forster and E. Pansardi for helping in the determinations.

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# *A Method For Recording Electromyograms in Man<sup>1</sup>*

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THIS ARTICLE describes a method whereby the electrical activity associated with denervated muscle in man can be studied at the bedside with the use of minimal apparatus and without the necessity of electrostatic shields. The apparatus and methods used and the equipment employed in testing the method together with sample electromyograms obtained from laboratory animals and from man are presented. The limits of usefulness and the degree of accuracy obtainable under hospital conditions are demonstrated and discussed. The apparatus used permits permanent photographic records to be obtained either directly from the fibrillating muscle or indirectly from the wire recording; such records are compared.

When the frequencies and amplitude of prolonged electrical activity were under study, permanent records were made on bromide paper. When detailed studies of the wave form of single action potentials were required permanent records were made on 35 mm. film. It should be emphasized that in the examination of patients only the electrode, one amplifier, the speaker and the wire recorder need be used. These are readily portable and can be used at the bedside without shielding because advantage is taken of the in-phase rejection input circuit by Toennies (1).

## METHOD OF RECORDING AND REPRODUCING

Reference to the block diagram, figure 1, will make clear the essentials of the system. Concentric needle electrodes of the type previously described were used (2). In recording from rat muscles a no. 27 hypodermic needle, one-half inch long, containing an insulated core of 40-gauge nichrome wire (.08 mm. diam.), was used. For use in human muscles the electrodes consisted of a no. 25 hypodermic needle, one and one-half inches long with a core of 32-gauge copper wire (.02 mm. diam.). The action potentials picked up by one of these electrodes were amplified by either of two preamplifiers *A* or *B*. To the output of one of these preamplifiers is connected

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the horizontal deflection plates of one C-R tube for photography, the vertical deflection plates of a second tube for visual observation, and the final stage of amplifier C. A 60-cycle sine wave on a third C-R tube provides a time base for the photographic record on paper. The output of amplifier C is connected to both the wire recorder and a loud speaker. It should be noted that the output circuit to the wire recorder contains a resistance-capacity coupling which partially compensates, at both extremes of frequencies encountered, for the characteristics of the wire recorder.

The combined capacitive output load at the oscilloscopes, when using preamplifier A, results in an 8.5% drop in voltage at 1200 cycles, a 24% loss

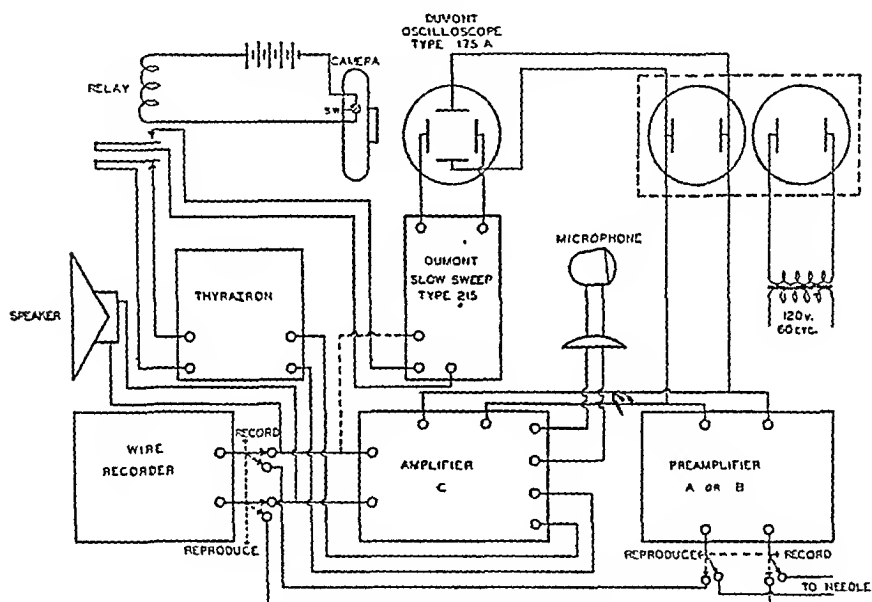


Fig. 1. BLOCK DIAGRAM of apparatus

at 1800 cycles and 37% loss at 2400 cycles. This preamplifier, because of small capacitive coupling, also shows a loss of 13% at 300 cycles. Preamplifier B with the same load is flat in response from 20 to 2000 and shows a loss of 5.5% at 3000 cycles.

Special mention should be made of the input circuit which is identical in the two preamplifiers. This is an adaption of the Toennies differential input circuit referred to above. It favors out-of-phase over in-phase potentials in the ratio of about 1000 to one and renders shielding of patients unnecessary. Interference is virtually nil when an indifferent grounded electrode is attached to the body.

### *Wire Recorder*

A model A 'Wirecorder'<sup>2</sup> was rebuilt. The recording head was removed from the reciprocating mechanism and relocated in a fixed position. The head was encased in heavy iron to shield it from magnetic fields set up by the motor, and was mounted on the chassis with rubber. Two brass pulleys were added to direct the wire uniformly through the recording head.

Identification of recording on the wire was accomplished by the use of a microphone into which numbers or commentaries could be spoken as the fibrillation record was being made. The locations on the wire at which either continuous paper records or single trace photographs had been made were easily found for reproduction by means of a metering device. For precise marking of the wire, both for photographic paper records and single trace pictures, a pulse generator was used. At the beginning and end of a continuous paper record the thyatron was tripped manually, generating a single pulse which appeared both on the paper and on the wire.

In making single trace photographs of individual complexes a switch synchronized with the camera shutter was used to control a relay which in turn closed the manual sweep circuit on the oscilloscope and also tripped the thyatron. By this means a pulse was placed on the wire immediately preceding the photograph of the single complex. This pulse was used later to trip the sweep for reproduction. A dotted line in the block diagram between amplifier C and the sweep indicates the connection necessary for this purpose.

### *Calibration*

For purposes of voltage calibration in the comparison of the original record and the reproduction, a 1000-cycle sine wave signal at 500 microvolts was used. The preamplifier was adjusted to give a deflection of 50 mm. on the oscilloscope both during recording and reproduction. In studying the characteristics of the wire recorder at various frequencies, calibrations were made with a sine wave generator. Preamplifier B, with an essentially flat response throughout the critical range, was used in this frequency calibration. Measurements were also made with an abrupt transient in the form of a partially damped wave at 1000 cycles. This transient of known initial polarity and voltage was produced by interruption of the current flow through the primary coil of a transformer; the secondary coil was coupled through a voltage-dividing network to the amplifier. The wave form in this case was determined by the inductance and distributed capacity of the

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<sup>2</sup> Obtained from WiRecorder Corporation, 1807 Stroh Building, Detroit 26, Mich. Any of the presently available wire or tape recorders would be satisfactory providing suitable compensation be made for the frequency response of the instrument selected.

transformer together with the resistance and capacity of the amplifier input circuit.

### RESULTS

Calibration (fig. 2) consists of single-trace photographs of the sine wave signals as recorded on and reproduced from the wire. It will be seen that there is no significant distortion of a sine wave within this frequency range.

Figure 3 is a curve showing the percentage voltages delivered from the wire after recording a sine wave at the given frequencies. The voltage delivered at 1000 cycles was arbitrarily considered as 100 per cent. The

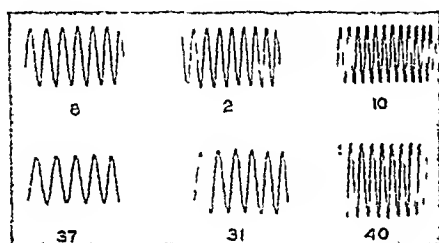


Fig. 2. SINGLE TRACE PHOTOGRAPHS of sine wave signals. Originals above; reproductions from wire below. Frequencies from left to right: 800 cycles; 1000 cycles; 1500 cycles.

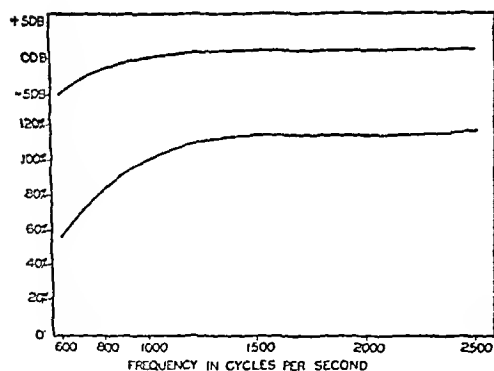


Fig. 3. CURVE SHOWING FREQUENCY RESPONSE of wire recorder and compensating circuit plus final stage of amplifier C; 1000 cycles is taken as 0 DB on the upper curve and as 100% on the lower curve.

above calibration was made using amplifier *B* and the value at 2500 cycles was corrected for the double loss in passing through the amplifier twice, since at this frequency only, in the range covered, did amplifier *B* deviate significantly from a flat response. This curve represents the frequency response of the wire recorder when supplied by the final power stage of amplifier *C* through the compensating circuit. The rather rapid falling off of the response of the system at low frequencies may give the impression that its sensitivity to an E.M.G. frequency of say 10 per second will be lowered. A moment's reflection will reveal that this 10 per second is not really the frequency of the complex itself but is its frequency of repetition. The spike



complex itself is a composite wave form, made up of several frequencies, all within the range of relatively flat frequency response for the system. It

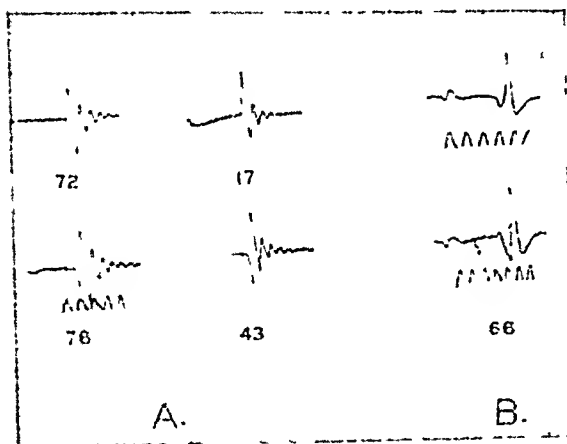


Fig. 4. A. SINGLE TRACE PHOTOGRAPHS of the test signal delivered to and reproduced from the wire using amplifiers A and B. Originals above; reproductions from wire below. Amplifier A left; amplifier B right. B. Fidelity of wave form of single complexes from man. Originals above; reproduction from wire below.

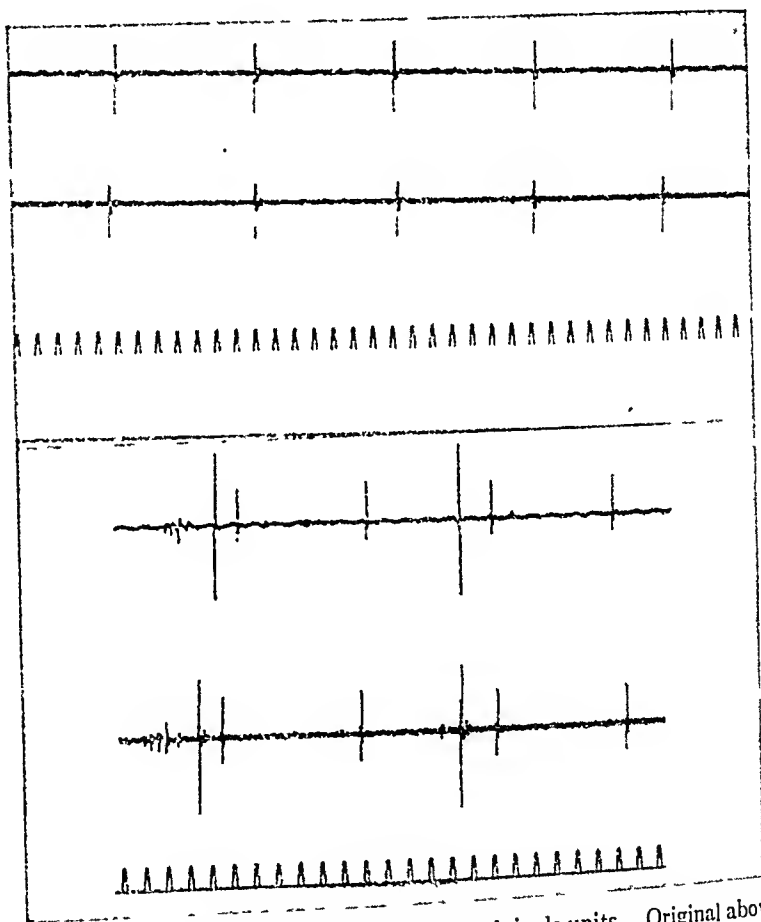


Fig. 5. A (top). MOVING PAPER PHOTOGRAPHS of single units. Original above; reproduction from wire below. B (bottom). MOVING PAPER PHOTOGRAPHS of multiple units. Original above; reproduction from wire below.

was noted that there was a progressive decrease in voltage delivered from the wire during the first two or three reproductions. After several repl

there was no further loss and the total voltage decrease did not exceed 10 per cent.

On careful analysis of single, essentially monophasic complexes from muscle, the wire reproduction was seen to include a small deviation of reversed polarity preceding the primary spike. The use of transient signals with a frequency within the range of that for muscle spikes and with known initial polarity established this as an artefact (see DISCUSSION).

Figure 4a consists of single-trace photographs of the test signal delivered to and reproduced from the wire using each of the two preamplifiers.

### *Fibrillation*

Figure 5 includes moving paper photographs from the oscilloscope showing the original spikes as recorded on the wire, and the reproduction from the wire. It will be seen that the reproduction is entirely adequate for the identification of discharge rates, both in the record of a single unit as in trace *a*, or in the case of multiple units as in trace *b*. Voltages may be compared with fair accuracy.

The degree of fidelity in wave form of single complexes can be seen by comparing the two single-trace photographs in figure 4b. The original was recorded from the paralyzed deltoid muscle of a man with a presumptive diagnosis of damage to the brachial plexus eleven months previously. The reproduction shows essentially the same wave form with only minor distortion of the first downward deflection.

### DISCUSSION

We have found the wire recorder of considerable value as a means of obtaining records in the study of fibrillation. Its use makes it unnecessary to stop for photography while systematically exploring muscles. Significant results can be photographed later if permanent records are desired, thereby saving both photographic material and labor. By repetition of the record significant changes may be noted which were missed previously. It makes unnecessary elaborate oscillographic equipment in the clinic and yet provides a record which is permanent for as long as desired. The wire, of course, may be used repeatedly. The reproduction from the wire is sufficiently accurate for any study of discharge rate and relative voltage which would be required in clinical electromyography. This includes the recording of fibrillation as well as fasciculation and electrical activity of innervated muscle.

For the detailed study of single complexes the wire recorder is of limited value by reason of the artefact referred to above. Camras (3) has examined in detail the magnetic phenomena in wire recorders, when continuous sinusoidal waves are recorded. He makes no mention of the artefact described above. This artefact consists of an additional wave of opposite sign to that

recorded and preceding the true wave. If one considers the flux distribution within the wire immediately in contact with the recording pole pieces, as illustrated by Camras, it is clear that this longitudinal segment of the wire becomes essentially a bar magnet (4). Each end of this magnet in turn will set up lines of force which establish an opposite pole in the adjacent segment. Upon reproduction this marginal segment will produce a deflection preceding and in a direction opposite that of the original signal. The density of magnetic flux responsible for this marginal field depends upon the rate of development of the primary signal field in relation to the rate of travel of the wire. The artefact is therefore prominent in the case of the test signal in which the initial gradient of deflection is maximal. For spikes recorded from muscle this is not the case. The initial deflection follows an exponentially rising potential. As a result the artefact is small. In fact the small, relatively slow, downward deflection preceding the main spike in figure 4b has essentially no artefact preceding it. It is only the abruptly rising potential of the main spike which has produced a small artefact seen to contribute to the preceding downward deflection. By using amplifier A which, under recording conditions, attenuates frequencies above 1000 cycles, it was possible to minimize the artefact produced by the wire. This amplifier, because of its attenuation below 400 cycles, also tends to minimize 60-cycle interference. The use of concentric electrodes allows good recording to be accomplished at lower amplifications than is the case with a unipolar electrode. It is true that the unipolar electrode automatically provides an essentially monophasic complex from muscles. The greater uniformity in the complexes would appear to have some advantage in estimating the degree of artefact obtained from a wire recording. This advantage, we feel, is offset by the increased tube noise and interference likely to be encountered at higher amplifications.

#### CONCLUSION

A new method for electromyography involving the use of a wire recorder is described. The advantages of the method are discussed. An analysis of the limitations of the method is presented together with recordings and reproductions of fibrillation and test signals used in this study.

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## *Man's Ceiling as Determined in the Altitude Chamber*

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THE DETERMINATION OF MAN'S TOLERANCE of anoxia has decreased in practical importance since the advent of pressurized aircraft, but scientific interest in questions of this sort has not waned. Many such investigations carried out during the war have been published. Thus, Dill and Hall (1) described pulmonary gas exchange, first breathing air at increasing altitudes until near breakdown and then breathing pure oxygen at much higher altitudes until a comparable end-point was reached. In that study, an altitude of 17,600 feet breathing air was found to correspond closely in gas exchange to 44,000 feet breathing oxygen.

The present experiments were carried out in April and May 1942. It was the intention, while breathing oxygen, to increase the altitude closer to the point of failure and to continue the experiments long enough to determine if a steady state could be reached. The goal was set at 45,000 feet, but a subsequent test of the altimeter showed an error of 200 feet; the actual pressure measured with a mercury manometer being 112 mm., equivalent to 44,800 feet.

### METHODS

Eight subjects participated in the experiments, the authors acting as observers and, also, in one case as subjects. The other 6, all young officers

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<sup>1</sup> At the time of these experiments, April and May 1942, Major, A.C., and in charge of the Physiological Branch, Aero-Medical Laboratory. At present, Scientific Director, Medical Division, Army Chemical Center, Maryland.

<sup>2</sup> At the time of these experiments, a member of the staff of the Physiological Branch, Aero-Medical Laboratory. At present, Assistant Professor of Physiology, Boston University School of Medicine, 80 East Concord Avenue, Boston, Mass.

or enlisted men, are listed below; thanks are due them for their willing participation:

Lt. F. W. Jache, AC (2 experiments)	S/Sgt. Green
Capt. J. J. Smith, MC	S/Sgt. Hohenshilt
S/Sgt. Fogelsanger	S/Sgt. Walker

There are two limiting factors in such experiments—anoxia and aeroembolism. In order to minimize the latter, a systematic procedure for eliminating gaseous nitrogen from the body was followed. Each subject, before ascent, breathed 100 per cent oxygen first while exercising on the bicycle ergometer and then while resting. Usually the work period and the rest period were each 30 minutes, although this varied somewhat being less for subjects known to be resistant to aeroembolism. Ascent began with the subject still breathing 100 per cent oxygen. It was standard practice to level off for a few minutes at 30,000 feet to complete preparations and to observe pulse rate and respiratory minute volume. The subsequent course will be evident from the data to be presented.

In some experiments the Millikan oximeter was used to give an approximate idea of the trend in arterial oxygen saturation. In each experiment an arterial blood sample was drawn, transferred under oil and heparinized. The methods used for determining gaseous contents, tensions, and capacity and  $pH$  were as follows:

CO<sub>2</sub> and O<sub>2</sub> content by Van Slyke.

O<sub>2</sub> capacity by equilibrating 4 ml. at room temperature and air; analysis by Van Slyke and correction for dissolved oxygen.

CO<sub>2</sub> capacity by equilibration of 4 ml. at body temperature and near the expected pCO<sub>2</sub> and pO<sub>2</sub> of the arterial blood. The CO<sub>2</sub> content (by Van Slyke) is a point on the carbon dioxide dissociation curve and can be used by familiar methods for calculating arterial pCO<sub>2</sub> and  $pH$ .

O<sub>2</sub> content by Van Slyke on the same sample; this, after correction for dissolved oxygen and division by the O<sub>2</sub> capacity gives a point on the oxygen dissociation curve. From this point and the arterial O<sub>2</sub> content, the arterial pO<sub>2</sub> is calculated.<sup>3</sup>

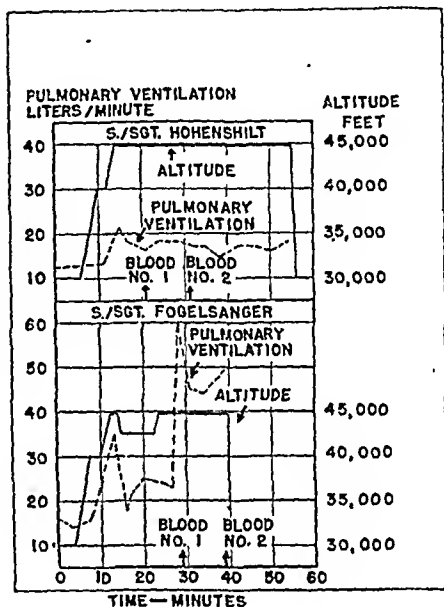
While the foregoing description is much condensed, further elaboration is out of place here. For further details, the reader is referred to Peters and Van Slyke (2), Henderson (3) and to the series of papers published by Henderson and associates in the *Journal of Biological Chemistry* from 1921

<sup>3</sup> This statement applies only to low arterial oxygen saturation where the steepness of the oxygen dissociation curve reduces the error of estimating pO<sub>2</sub>. For example, assume the oxygen combining capacity is  $20 \pm 0.2$  vol. %, the combined oxygen is  $13 \pm 0.2$  vol. % and the  $pH$  7.5. The oxygen saturation lies between 63.4 and 66.7% corresponding to arterial pO<sub>2</sub> values of approximately 30 and 32 mm. Hg, respectively. Between 90 and 93% saturation the corresponding range in pO<sub>2</sub> would be about five times as great.

to 1937 on "Blood as a Physiochemical System." These analyses and calculations antedate the demonstration by Roughton and associates (4) that the method for oxygen saturation is slightly in error, giving a saturation about 2 per cent low; if a correction is applied, the arterial oxygen saturation would be raised about 2 per cent and the  $pO_2$  about 2 mm. Hg.

In each experiment the subject breathed oxygen from a system that insured no admixture with chamber air. At times he used a mouthpiece

Fig. 1. RESPIRATORY RESPONSES of 2 subjects breathing 100%  $O_2$  at 44,800 ft. S/Sgt. Hohenshilt represents an av. response—pulmonary ventilation of 15 to 20 l/min. at 37° C., saturated and ambient pressure. The other subject was consciously hyperventilating.



and nose clip and his expired air was collected in a gasometer. These collections of expired air provided a measure of pulmonary ventilation.

## RESULTS

The respiratory responses of 2 subjects are shown in figure 1. One of these, Hohenshilt, had an average response, while the other, Fogelsanger, was consciously hyperventilating. The respiratory and circulatory responses of Penrod, who represents the opposite extreme in respiratory response from Fogelsanger, are illustrated in figure 2.

Related properties of arterial blood for all 8 subjects, including the above 3, are found in table 1. The last column of this table gives the differences between the ambient pressure and the sum,  $pCO_2$ ,  $pO_2$  and  $pH_2O$  of arterial blood. If there were complete equilibrium and no error in determination, these should balance, the difference being zero. The fact

that the figures with the exception of one zero are positive will be discussed later.

Figures 3 to 6 record the notes taken by one of us (DBD) during the latter part of the longest exposure to 44,800 feet. The handwriting is

Fig. 2. RESPIRATORY AND CIRCULATORY RESPONSES of Penrod before and during an exposure to 44,800 ft. This subject had an av. response in pulse rate, the lowest respiratory response, reached one of the lowest arterial saturations and had the most unpleasant after-effects (see text). The record of arterial oxygen saturation is from Millikan oximeter measurements; the pulse rate is from the cardi tachometer.

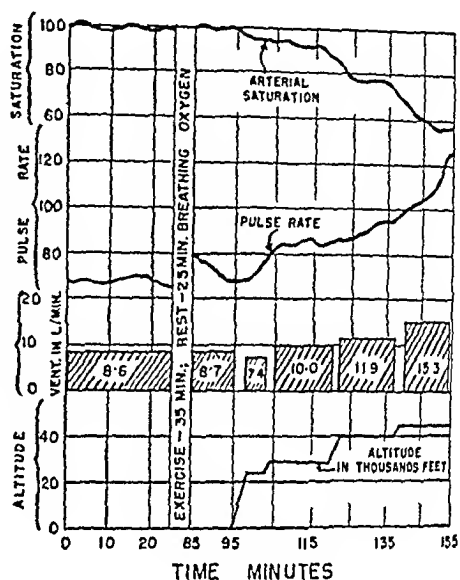


TABLE 1. ARTERIAL BLOOD AT 44,800 FEET (112 MM. Hg)

SUBJECT	OXYGEN SATURATION	pO <sub>2</sub>	pCO <sub>2</sub>	pH	Δp <sup>1</sup>
	%	mm. Hg	mm. Hg		mm. Hg
Penrod.....	62.3	31	34	7.45	0
Dill.....	66.5	30	29	7.51	6
Jache.....	58.1	27	30	7.51	8
Green.....	69.3	29	24	7.61	12
Walker.....	62.7	27	25	7.55	13
Smith.....	60.4	29	28	7.53	8
Hohenshilt.....	67.9	29	24	7.59	12
Fogelsanger <sup>1</sup> .....	83.9	37	12	7.76	16

<sup>1</sup> This subject by conscious hyperventilation reached a minute volume of 56 liters during the puncture.

<sup>2</sup> Ambient pressure minus the sum of arterial pO<sub>2</sub>, arterial pCO<sub>2</sub>, and arterial pH<sub>2</sub>O.

somewhat poorer than usual, but is legible and the meaning is clear, except for one error in writing '4' for '42' (fig. 6).

## DISCUSSION

The foregoing results extend considerably the experiments of Dill and Hall (1). A higher altitude was reached, significant measurements of respiratory volume were made, the exposure was longer and the number of

Time - 18 minutes at 44,800 feet. This record being written by Major D.B. Dill after ascent in company with Sgt. George Hohenschilt. Both of us breathed oxygen while exercising on bicycle ergometer at ground level and continued so during ascent to 30,000 feet. During this time, D.B.D. wore the Hishbark adaptation of the A2 mask (otherwise referred to as the A8A adaptation). Sgt. H wore the same mask and both were attached to the Pioneer demand valve. Sgt. H. wore the cardiorespirator leads and test oximeter units. At 30,000 feet he shifted to a Kugel valve this being served

→ 2.

(T = 26 min)  
 Play the same Pioneer demand and valve.

Tests of the oximeter with as to nose on, off and emergency on were made to adjust to 100 % saturation thus ensuring minimal errors.

Ascent was then made to 35,000 without incident.

After leveling off here for 3 minutes ascent continued to 40,000 feet and all going well to 44,800 ft.

At 44,800 ft Major Dill shifted to the emergency on to insure maximal efficiency.

After 5 min at 44,800 feet there was attempted one self radial.

Post 3 -  
 Potted 29-32 min for note by Sgt. H  
 was similar to previous exposure  
 after 30-32 min  
 Note by Sgt. H at 44,800  
 after 30-32 min  
 Disappeared after stamp and feel  
 head clear. Returned on same  
 both long and relief fully.  
 Time 30.

Note continued  
 Poor radial function  
 Sincere feel breathless  
 at 35 min - air  
 samples

at 41 min samples  
 incomplete

Pear D. = 104

S. = 88

D. = 100

4 Min - Start down

- Written during descent

During 41 - 3 min  
 Dill counted pulse on  
 Sgt. H with some difficulty  
 finally getting recorded  
 count of 88. Then he  
 counted his own and  
 got 104. Sgt. H. checked  
 this with a count of 100.

During 35 min on  
 D developed some bands  
 slight joint pain. At  
 41 min gas thing became  
 somewhat painful.  
 Bronchial discomfort was  
 more evident on descent

Fig. 3 (upper left). FIRST SHEET of notes kept by one of the authors (Dill) on the occasion of the longest exposure (42 min.) to 44,800 ft. There is only one mistake on this page—failure to close the parentheses.

Fig. 4 (p. 2). SECOND SHEET of notes. The writing is more scraggly and there are two mistakes—'adust' for 'adjust' and failure to record which radial was first attempted.

Fig. 5 (p. 3). THIRD SHEET of notes, partly by Sgt. Hohenschilt. He writes, "Nose hurt due to pressure and sunburn. Left ear unit too tight but bearable. Slight —? and of left foot asleep up to — knee. Alseep. Vision not impaired. . . . Disappeared after stamping. . . ." P on D refers to a pulse count on Dill.

Fig. 6 (p. 4). '4 MIN.' SHOULD READ '42 MIN.' The remainder of this page was written during descent with normal oxygen saturation but with residual aeroembolism.

subjects was greater. While increasing the altitude by 800 feet is of negligible physiological importance at somewhat lower barometric pressures, it represents a very considerable added strain under the circumstances of these



experiments. Decreasing the barometric pressure from 116.3, equivalent to 44,000 feet, to 112.0 mm. Hg involves a decrement in  $pO_2 + pCO_2$  of alveolar air of 4.3 mm., or 6 per cent.

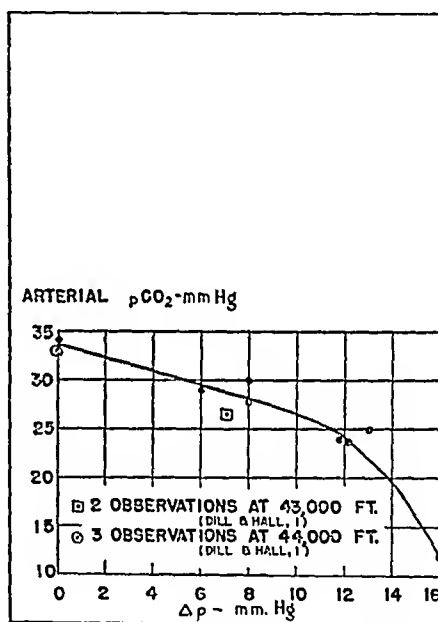
This change in alveolar air calls forth a response in respiratory regulation—minor in some individuals and major in others. The 8 subjects studied illustrate extreme of response, e.g. Penrod, who showed minimal decrease in alveolar  $pCO_2$  and Fogelsanger who, by consciously hyperventilating, reached a pulmonary ventilation of 56 l/min. at the time the arterial puncture was made. The intermediate values were more like Penrod's than Fogelsanger's and the composition of arterial blood reflected these differences. With the exception of Fogelsanger, arterial  $pCO_2$  and  $pH$  averaged 27.7 and 7.54 respectively, the ranges being 24 to 34 and 7.45 to 7.61. The arterial oxygen saturations in the same 7 men ranged from 58.1 to 69.3 and averaged 63.9. By contrast, Fogelsanger's arterial oxygen saturation was 83.9 per cent, a value characteristic of about 42,000 feet. This high saturation was associated with an arterial  $pCO_2$  of 12 and a  $pH$  of 7.76.

In brief exposures to high altitudes, no sharp limit can be set defining where hyperventilation begins. As shown above, the response varies greatly from one individual to another. In line with this, Dill and Hall (1) reported that 3 subjects breathing 100 per cent oxygen at 44,000 feet had a considerable increase in ventilation, 2 at 43,000 feet had even more stimulation to breathing, while 2 at 42,000 feet had no considerable change. At 40,000 and 41,000 feet the effect on breathing was considerable in some and negligible in others. It is emphasized that these observations apply to *brief* exposures only. In residents at high altitude, there appears to be an ultimate respiratory adjustment to very slight reductions in ambient oxygen tension. The experiments of Fitzgerald proved this many years ago (5).

The last column of table 1 shows the difference between the total ambient pressure (which is also essentially the total pressure in the alveoli) and the sum of partial pressures of oxygen, carbon dioxide and water vapor in arterial blood. It can be assumed almost with certainty that the alveolar air even during hyperventilation becomes fully saturated with water vapor. The figures given in this column, hence, are the amounts by which the  $pCO_2 + pO_2$  of alveolar air exceed the  $pCO_2 + pO_2$  of arterial blood. It will be noted that this ranges from zero in the case of Penrod, who had the lowest alveolar ventilation, to +16 in Fogelsanger, who had maximal ventilation. There is not a straight-line correlation between alveolar ventilation (as indicated by diminished arterial  $pCO_2$ ) and this difference, but the trend is in that direction. That is, the greater the alveolar ventilation the greater the discrepancy between  $pCO_2 + pO_2$  of arterial blood and of alveolar air.

A reasonable hypothesis can be advanced to explain this phenomenon. The differences are positive, implying that  $p\text{CO}_2$  or  $p\text{O}_2$ , or both, are larger in alveolar air than in arterial blood. Since the movement of  $\text{CO}_2$  is outward, it cannot attain a higher partial pressure in the alveolar air than in the arterialized blood. Actually there is a mass of evidence indicating that  $\text{CO}_2$  diffuses far more rapidly than oxygen; in healthy individuals, regardless of activity, of rate of ventilation or of circulation, it attains virtually complete equilibrium as the blood passes through the alveolar capillaries. This is supported by experimental determinations of arterial-alveolar  $\text{CO}_2$

Fig. 7. RELATION OF  $\Delta p$  TO ARTERIAL  $p\text{CO}_2$ . The former is believed to measure the gradient of oxygen across the alveolar membrane; the latter gives a reciprocal measure of alveolar ventilation. Although the number of measurements at 44,800 ft. is small, the correlation between  $\Delta p$  and  $p\text{CO}_2$ ,  $-0.88$ , is highly significant. The curve is drawn free-hand to represent the trend.



gradients dating back to those of Bock and Field (6) with the same techniques used in this study. Hence it is highly improbable that the present phenomenon can be interpreted in terms of  $\text{CO}_2$ . According to past experience, the experimental error in determining arterial  $p\text{CO}_2$  and arterial  $p\text{O}_2$ , under the conditions of these experiments, does not usually exceed  $\pm 2$  mm. for either variable. By elimination, it follows that the figures given in the last column of table 1 correspond approximately to the gradient of oxygen from alveolar air to arterial blood.

In order to visualize the relation between  $\Delta p$ , the presumed gradient of oxygen from alveoli to blood, and the alveolar ventilation,  $\Delta p$  has been plotted as a function of arterial  $p\text{CO}_2$  in figure 7. The latter variable bears a sort of reciprocal relation to alveolar ventilation; in view of the rapid

diffusion of  $\text{CO}_2$ , this relation probably is an intimate one. It appears from figure 7 that so long as the alveolar ventilation does not lower the arterial  $\text{pCO}_2$  more than 5 mm. Hg, the gradient of oxygen across the alveolar membrane is small, not exceeding 6 mm. On the other hand, with higher ventilation and with associated decrease in arterial  $\text{pCO}_2$  to 30 or below, the gradient increases up to 16 mm. Hg. In other words, the gain in arterial oxygen saturation arising from hyperventilation is partially offset by the decreased efficiency of oxygen uptake. Whether this phenomenon has some simple physiological explanation remains to be determined. It may relate to a reduction in time available for attainment of equilibrium or it may have a physicochemical basis such as a slowed rate of reaction between oxygen and hemoglobin at the higher pH values.

TABLE 2. EQUIVALENT ALTITUDES BREATHING AIR AND BREATHING OXYGEN CORRESPONDING TO SIX PHYSIOLOGICAL STATES

PHYSIOLOGICAL STATE	ARTERIAL $\text{pO}_2$	ARTERIAL OXYGEN	EQUIVALENT ALTITUDES	
			Breathing air	Breathing oxygen
	mm. Hg	% saturation	ft.	ft.
Usually normal.....	70	93	6,000	37,600
Anoxia measurable; sometimes detectable subjectively, particularly in exercise.....	60	90	8,000	39,100
Appreciable handicap.....	50	84	10,800	40,900
Considerable handicap.....	40	77	14,600	43,100
Serious handicap.....	35	71	17,600	44,000
Imminent collapse.....	30	66	19,000	44,800

The performance of the 8 individuals during and after the exposure to 44,800 feet is of some interest. No one lost consciousness and only one, Fogelsanger, became slightly tetanic. The increases in heart rate and respiratory rate were what one expects in this range of anoxia, except for the one subject who consciously hyperventilated. Only one individual, Penrod, experienced after-effects probably related to anoxia. After both runs he developed a severe headache and, in one case, scintillating scotomata with nausea. This intensity of anoxia, if long-continued, certainly would have resulted in headache in most individuals; no doubt the shortness of the exposure accounts for the freedom from after-effects in 7 of the 8 who took part. There was some evident loss of efficiency, as is indicated by the errors shown in figures 3 to 6. However, it would be incorrect to assume, on the strength of the absence of gross errors that the members of a crew of an unpressurized aircraft could operate safely at this altitude. The physical hazards and the associated emotional strain would be immeasurably greater. The subjects here were under constant surveillance by experienced personnel

stationed outside the chamber; in case of an accident, normal atmospheric conditions could have been restored in less than one minute. Errors that were trivial in the chamber might have been fatal in an aircraft. It is safe to state that an experienced pilot might be able, without pressurization, to fly at 44,800 feet for 40 minutes, but the hazard would be considerable, even with perfect oxygen equipment.

An attempt has been made in table 2 to describe the physiological states in terms of altitude. This represents an extension and modification of figure 1, Dill and Hall (1). The last column gives the critical altitudes when pure oxygen is breathed and the preceding column gives corresponding altitudes when air is breathed.

These experiments illustrate a principle adopted by Captain Harry G. Armstrong<sup>4</sup> and his associates when the Aero-Medical Laboratory began functioning in 1937; viz., in hazardous human experimentation, those who plan the experiments should be the first to participate as subjects. This principle has guided the research program of the Aero-Medical Laboratory through the war years and since. It is the authors' conviction that it might well be accepted as a guiding principle in physiological research pertinent to this Journal.

#### SUMMARY AND CONCLUSIONS

Eight men exposed in the pressure chamber to a simulated altitude of 44,800 feet illustrated a wide range in reactions. Arterial oxygen saturation ranged from 58 to 84 per cent, arterial  $p\text{CO}_2$  from 12 to 34 mm. Hg, and  $p\text{H}$  from 7.45 to 7.76. No one lost consciousness and only one became slightly tetanic. One of the 8 experienced after-effects attributable to anoxia. At the same time, all were in a state of imminent collapse.

It appears that the pressure gradient of oxygen from alveoli to arterial blood increases in the hyperventilation of severe anoxia. In the instance of extreme hyperventilation—56 l/min.—this gradient was 16 mm. Hg.

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# *Tolerance of Normal Men to Explosive Decompression<sup>1</sup>*

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WORK DONE IN THIS LABORATORY and already reported has shown that laboratory animals tolerate explosive decompressions over ranges of as much as three quarters of an atmosphere and at rates of pressure changes as great as 650 psi per second (1). While such explosive decompressions may cause hemorrhages in the lungs, heart and brain, these lesions are of minor importance and are not associated with any detectable disability (2). These experiments are presumptive evidence that human beings would tolerate similar explosive decompressions. However, in view of the increasing use of pressurized aircraft in civilian as well as in military aviation, it seemed desirable to determine directly the effects of explosive decompression on man.

Since a pressurized aircraft might be unable to descend to lower altitudes following explosive decompression (as for instance in flying over mountain ranges) the passengers and crew would possibly be subjected not only to the hazard of the explosion itself, but also to the effects of exposure for some time to a reduced barometric pressure. These experiments have therefore been designed not only to test the tolerance of normal subjects to explosive decompression but, also to determine the effect of explosive decompression on the incidence of and susceptibility to decompression sickness.

## METHODS

Experiments were carried out in a decompression chamber consisting of a smaller chamber, or air-lock, and a larger or main chamber. For purposes of these experiments, the lock represented the pressurized aircraft cabin, while the main chamber represented the ambient atmosphere. The door between the lock and the main chamber was provided with an aperture whose diameter could be varied by the insertion of a series of machined metal rings. A cellulose acetate membrane sealed across the aperture served to separate the two chambers. The subjects, provided with oxygen equipment of the

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<sup>1</sup> The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Ohio State University Research Foundation.

diluter-demand type, entered the lock, a desired pressure differential was established between the lock and the main chamber and explosive decompression was produced at the desired instant by passing an electrical current through a nichrome wire sealed to the membrane with scotch tape. The heat of the wire caused the membrane to rupture. The rate of the decompression could be varied by changing the size of the aperture and the range of decompression was determined by the pressure differential existing between the lock and chamber prior to the rupture of the membrane.

In all, 150 subjects were employed, the majority ranging in age from 18 to 25 years, although subjects as young as 16 years and as old as 56 years took part in the experiments

TABLE 1. SUMMARY OF EXPERIMENTS

RANGE OF SIMULATED ALTITUDES	RANGE OF PRESSURES	DECOMPRESSION TIME	DECOMPRESSION RATE	NO. OF SUBJECTS	NO. OF DECOMPRESSIONS
<i>ft.</i>	<i>mm. Hg</i>	<i>sec.</i>	<i>mm. Hg/sec.</i>		
8,000-35,000	564-179	2.2	175	10	13
		1.3	296	10	13
		0.6	642	10	15
		0.4	963	13	30
10,000-27,000	523-261	1.5	175	14	46
		0.2	1310	14	19
10,000-35,000	523-179	2.0	43	14	36
		2.0	172	29	90
		0.3	1147	4	4
10,000-40,000	523-141	8.9	43	2	2
		2.2	174	3	3
20,000-35,000	349-179	4.5	38	22	22
		1.1	155	3	3
20,000-40,000	349-141	5.5	38	49	66
		1.4	149	82	91
		0.7	297	4	8
		0.3	693	2	7
		0.2	1040	8	20
27,500-45,000	253-111	2.0	71	20	66

A summary of the experiments including a listing of the number of subjects used at each rate and range is given in table 1.

## RESULTS

*General Tolerance.* In more than 500 experiments on 150 subjects, explosive decompressions at rates as fast as 1300 mm. Hg/sec. and over ranges of more than half an atmosphere caused no apparent ill effects.

Subjective sensations reported were a rush of air from the nose and mouth, a feeling that the oxygen mask was being torn from the face, sudden abdominal distention and the sensation of a deep inspiration. There has been no case of difficulty in clearing the ears and abdominal gas pains were not significantly worse than those associated with slow decompressions.

Subjects were invariably able to carry on required activities following the decompression and no signs or symptoms directly referable to explosive decompression appeared during subsequent exposures of 15 to 90 minutes at low barometric pressures.

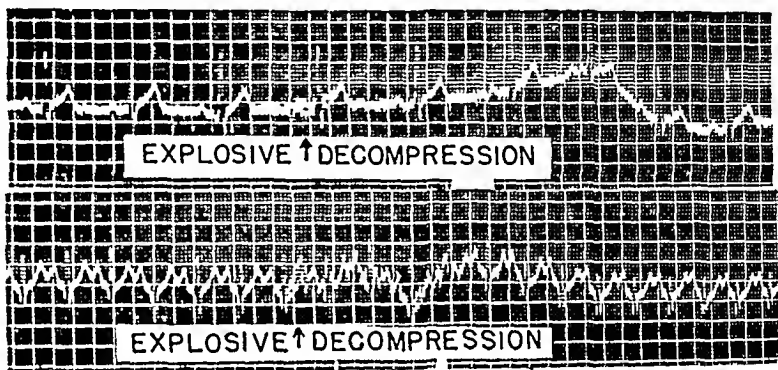


Fig 1 (*top*). HUMAN ELECTROCARDIOGRAM IN EXPLOSIVE DECOMPRESSION. Lead II. Decompression from 20,000 ft. to 40,000 ft. in 1.4 sec. (2.9 psi/sec.). There is no change in the e.c.g. Compare with fig. 2.

Fig. 2 (*bottom*). HUMAN ELECTROCARDIOGRAM IN EXPLOSIVE DECOMPRESSION. Lead II. Decompression from 20,000 ft. to 40,000 ft. in 1.4 sec. (2.9 psi/sec.). Extremely rapid heart rate due to apprehension. No change with decompression. Compare with fig. 1.

All the subjects listed experienced at least two explosive decompressions and exposure to as many as 50 such decompressions was without apparent effect.

*Electrocardiograms.* With the use of a General Electric electrocardiograph, records of Lead II were taken on 16 subjects decompressed from 349 mm. Hg (20,000 ft.) to 141 mm. Hg (40,000 ft.) in 1.4 seconds, and on 2 subjects decompressed from 564 mm. Hg (8000 ft.) to 179 mm. Hg (35,000 ft.) in 0.4 seconds. Most of these subjects showed a sinus tachycardia as the result of the apprehension associated with the experiment. This varied in degree with the subject's emotional make-up and was absent in some cases. No other changes were noted. Typical records are shown in figures 1 and 2.

*X-Rays of the Chest.* X-rays of the chests of 23 subjects explosively decompressed twice from 349 mm. Hg (20,000 ft.) to 121 mm. Hg (40,000 ft.) at rates as fast as 149 mm. Hg/sec. were taken before and after the series of decompressions. Similar chest plates were taken of 3 subjects each of whom had been explosively decompressed as many as 50 times at rates as

fast as 1147 mm. Hg/sec. and over ranges as great as 564 mm. Hg (8000 ft.) to 179 mm. Hg (35,000 ft.). All plates were made by the department of Radiology of the University Hospital, and read by its roentgenologist. In no case was there any evidence of pulmonary lesions following the experiments.

**Audiograms.** Audiograms of 33 subjects explosively decompressed at rates as great as 172 mm. Hg/sec. over ranges of 349 mm. Hg (20,000 ft.) to 141 mm. Hg (40,000 ft.) or 523 mm. Hg (10,000 ft.) to 179 mm. Hg (35,000 ft.) were taken with a Western Electric No. 6 audiometer before and after a series of three explosive decompressions. There were no significant changes in the hearing of any of the subjects.

TABLE 2. INCIDENCE OF INCAPACITATING BENDS

*Exposure to 179 mm. Hg (35,000 ft.) for one hour after explosive decompression from 349 to 141 mm. Hg (20,000 to 40,000 ft.). Thirty-three male subjects without exercise*

Rate of decompression . . .	SLOW RUNS		EXPLOSIVE RUNS	
	35 mm. Hg (0.7 psi)/min.	104 mm. Hg (2 psi)/sec.	208 mm. Hg (4 psi)/sec.	Both rates
No. of man runs.....	92	33	33	66
No. of incapac. bends . .	7	8	11	19
% incapac. bends . . . .	7.6	24.2	33.3	28.8
Av. time at altitude in min. . . .	57.9	54.6	51.7	53.2

**Incidence of Decompression Sickness Following Explosive Decompression.** In this phase of the investigation six groups of subjects were used. *Group I* consisted of 33 male medical students between the ages of 20 and 25, who were explosively decompressed from 20,000 to 40,000 feet (a range of 208 mm. Hg) with a subsequent stay at 35,000 feet for one hour without exercise. Each subject experienced one decompression at a rate of 38 mm. Hg (0.7 psi) per second and one at a rate of 150 mm. Hg (3 psi) per second. Twenty-six of the subjects had three and 7 had two control decompressions. The rate of decompression in these slow or control runs was approximately 35 mm. Hg (0.7 psi) per minute. Therefore the decompression to 35,000 feet (179 mm. Hg) required about 17 minutes.

The data for this group are shown in table 2. In 92 slow runs, there were 7 cases of incapacitating bends (7.6%); in 66 explosive runs there were 19 cases of incapacitating bends (28.8%). This difference in incidence is highly significant statistically. However, the difference between the two rates of explosive decompression is not statistically significant.

**Group II.** Because of the low incidence of incapacitating bends in the control runs of *Group I*, it was decided that a more severe test would be of advantage in determining the effect of explosive decompression on the



susceptibility to decompression sickness. Accordingly, the procedure used with *Group II* was as follows: each subject underwent two explosive decompressions at the same rates used with *Group I*. The range was in all cases from 20,000 to 40,000 feet (208 mm. Hg) with a subsequent stay at 38,000 feet for 90 minutes or until intolerable bends occurred. During the stay at altitude each subject did three knee bends and three push-ups with weights every 10 minutes. This exercise was recommended for use in bends studies by the Committee on Decompression Sickness. Each subject had three control runs in which they were taken to 38,000 feet in from 16 to 18 minutes. The data on this group are shown in part A of table 3.

TABLE 3. INCIDENCE OF INCAPACITATING BENDS

*Exposure to 155 mm. Hg (38,000 ft.) altitude for 90 min. after explosive decompression from 349 to 141 mm. Hg (20,000 to 40,000 ft.) C.D.S. exercise*

Rate of decompression .....	SLOW RUNS		EXPLOSIVE RUNS	
	35 mm. Hg (0.7 psi)/min.	38 mm. Hg (0.7 psi)/sec.	149 mm. Hg (3 psi)/sec.	Both rates
<i>A. 37 Male Subjects</i>				
No. of man runs.....	111	37	37	74
No. of incapac. bends.....	62	23	25	48
% incapac. bends.....	55.0	62.2	67.6	64.9
Av. time at altitude in min.....	65.3	60.3	54.8	57.6
<i>B. 6 Women Subjects</i>				
No. of man runs.....	12	12	12	24
No. of incapac. bends.....	7	7	6	13
% incapac. bends.....	58.5	58.5	50.0	54.1
Av. time at altitude in min.....	59.5	63.8	65	64.4

In 111 slow runs there were 62 cases of incapacitating bends (55%) and in 74 explosive runs there were 48 cases (64.9%). The chi square value indicates that this difference is not significant. If the two rates of explosive decompression are considered separately, there were 23 cases of incapacitating bends in 37 man runs at the slower rate (62.2%) and 25 cases out of a total of 37 man runs (67.6%) at the faster rate. These differences are not statistically significant.

It can be seen from the table that the total time spent at altitude is less with the explosive runs than with the slow runs. The 't' test for significance, applied to these figures, however, shows no significant difference.

*Group III* consisted of 6 women students between the ages of 15 and 24. The procedure for slow and explosive runs was the same as for *Group II*. Each subject had two control runs and two explosions at each of the two

rates used with *Group II*. The results are tabulated in part B of table 3. There were no significant differences in the incidence of incapacitating bends or in the average time at altitude between the slow and explosive runs.

*Group IV* was made up of 15 dental students who were subjected to three decompressions from 10,000 feet to 35,000 feet at the rate of 150 mm. Hg/sec. with a subsequent stay of 90 minutes at 38,000 feet. This was an increase of about 50 per cent in the range of the explosion. The routine exercise already described was used with this group. Each subject had three slow or control runs.

The results are shown in table 4. In 45 slow runs there were 28 cases of incapacitating bends (62.2%); in 42 explosive runs there were 36 cases

TABLE 4. INCIDENCE OF INCAPACITATING BENDS

Exposure to 155 mm Hg (38,000 ft) for 90 min. after explosive decompression from 523 to 170 mm Hg (10,000 to 35,000 ft) 15 male subjects CDS exercise

Rate of decompression	SLOW RUNS	EXPLOSIVE RUNS
	35 mm. Hg (0.7 psi)/min	208 mm. Hg (4 psi)/sec
No. of man runs	45	42
No. of incapac. bends	28	36
% incapac. bends	62.2	85.7
Av. time at altitude in min.	62.2	52.7

(85.7%). The chi square value for this difference is 6.16, which is significant. The total time at altitude after explosive decompression is less than that after slow decompression, and the 't' test applied to the average times for each subject for explosive and slow decompressions indicates that the differences are statistically significant.

*Group V*. In the four groups already discussed all subjects breathed 100 per cent oxygen from ground level up. There was thus a period of preoxygenation of 15 to 17 minutes before the final altitude was reached in slow runs and before explosive decompression in explosive runs. Experiments carried out on *Group V* were designed to eliminate this factor. Subjects, therefore, breathed from regulators with the Automix 'ON' in all runs. The range of explosive decompression was similar to that employed with *Group IV*. Twelve male and 2 female students were used as subjects in these experiments. Each subject had two or three control runs and was explosively decompressed twice at each of the two rates already described.

Subjects remained at altitude for the duration of the experiment or until they developed intolerable or incapacitating bends or were unable to perform the standard exercise.

Data obtained are summarized in table 5. In 32 slow runs there

were 21 cases of incapacitating bends (65.5%). In 50 explosive runs there were 33 cases of incapacitating bends (66%). In view of the significantly greater incidence of incapacitating bends in the explosive runs of Group IV, these results are somewhat surprising. An explanation is suggested, however, when one notes the relatively high incidence of incapacitating bends in the slow runs on this group (65.6%). It seems possible that the presence of a bends-producing factor in the control runs may mask the bends-producing tendency of explosive decompression.

TABLE 5. INCIDENCE OF INCAPACITATING BENDS

*Exposure to 155 mm. Hg (35,000 ft.) for 90 min. after explosive decompression from 523 to 179 mm. Hg (10,000 to 35,000 ft.). 12 male and 2 female subjects. C.D.S. exercise, no preoxygenation*

Rate of decompression .....	SLOW RUNS		EXPLOSIVE RUNS	
	35 mm. Hg (0.7 psi)/min.	104 mm. Hg (2 psi)/sec.	208 mm. Hg (4 psi)/min.	Both rates
No. of man runs.....	32	25	25	50
No. of incapac. bends.....	21	16	17	33
% incapac. bends.....	65.6	64.0	68.0	66.0
Av. time at altitude in min.....	53.0	53.4	54.5	54.0

*Group VI.* The sixth group of subjects was used in experiments designed to determine the effects of explosive decompression from altitudes not requiring pressure breathing to altitudes at which pressure breathing is necessary. It was hoped that these experiments would provide answers to the following questions:

1. Is explosive decompression to such altitudes harmful?
2. Is the duration of useful consciousness after such explosive decompression long enough to allow the subject to resort to pressure breathing?
3. Does such an explosive decompression and subsequent stay at such altitudes tend to be a factor in the production of gas pains, anoxia, circulatory collapse or any other untoward symptoms?

It was decided to employ an explosive decompression from 27,500 to 45,000 feet, a differential of 2.75 psi which is the pressure differential recommended for pressurized aircraft when in combat.

Subjects, equipped with A-13 pressure masks and A-16 pressure demand regulators, were taken to 27,500 feet in the lock and after a stay of 15 minutes were explosively decompressed to the final altitude of 45,000 feet in two seconds. They then entered the chamber and remained at 45,000 feet for one hour or until forced to descend. The subjects took no exercise during these decompressions. One hundred per cent oxygen at a pressure of two inches of water was breathed until just prior to the explosive

decompression at which time the pressure was decreased to 0. Immediately after the explosion the pressure was turned up to 8 or 10 inches of water. All subjects had taken part in previous experiments, were familiar with the regular oxygen demand apparatus and had already had experience in explosive decompressions. They were instructed in the use of pressure breathing equipment and were given an indoctrination run to 45,000 feet for several minutes with pressure breathing prior to the first slow experimental runs.

This series of experiments was begun with 28 potential subjects who were given a total of 30 indoctrination runs. In these runs the subjects were taken to an altitude of 45,000 feet and kept there for approximately five minutes. There were seven forced descents. Three of these were due to collapse, two to dizziness and one each to gas pains and nausea. In the three cases of collapse, the fainting was preceded by dizziness and it is our belief that these cases were not direct circulatory collapse, but were due to anoxia, perhaps complicated by hyperventilation and a consequent acapnia. Six subjects dropped out of the experiment at the end of the indoctrination runs and 7 of the remaining 22 failed to complete the experiments. A total of 11 slow runs were made on the 7 subjects who started but failed to complete the experiment. In no case did any of the subjects remain at 45,000 feet for the required 60 minutes. Four of them were forced down by bends, 1 by chokes, 2 by nausea, 3 by dizziness and 1 by collapse.

The results obtained on the 15 subjects who completed the experiments are shown in table 6. There were 32 slow runs and 29 explosive runs carried out on these subjects. It will be noted that there were 13 cases of bends (40.6%) in the slow runs as against 16 cases (55.2%) in explosive runs. The incidence of chokes is approximately the same in both slow and explosive runs. The other causes of descent (gas pains, dizziness, collapse etc.) occurred occasionally, but were too infrequent to justify any statement concerning them. There were only three cases of subjects who remained at altitude for the entire hour in slow runs as against four in explosive runs. The explosive decompression itself seemed to be without harmful effects. In all cases the subjects were able to switch to pressure breathing after the explosion without difficulty.

It might be expected that the incidence of incapacitating bends at 45,000 feet would be greater than at the lower altitudes employed in previous experiments. That this was not found to be the case is in the main due to the number of forced descents due to other causes, i. e. chokes, gas, nausea, vertigo and collapse.

It is also of interest that although the numbers are small, there was a

decrease in the forced descents due to causes other than bends or chokes following explosive decompression. This is attributed to the fact that explosive decompressions were performed after the indoctrination and at least two slow ascents. Therefore the subjects were more experienced in the use of pressure breathing equipment when subjected to the explosive decompressions. That experience is an important factor in such experiments is borne out by the fact that the subjects reported less distress and

TABLE 6. EFFECT OF EXPLOSIVE DECOMPRESSION ON THE ABILITY TO TOLERATE ALTITUDE REQUIRING PRESSURE BREATHING

*Exposure to 111 mm. Hg (45,000 ft.) for 1 hour after explosive decompression from 252 mm. Hg (27,500 ft.). No exercise*

RATE OF DECOMPRESSION	COMPLETED SLOW RUNS 33 MM. HG (0.6 PSI)/MIN.	EXPLOSIVE RUNS 208 MM. HG (4 PSI)/SEC.	RATE OF DECOMPRESSION	COMPLETED SLOW RUNS 33 MM. HG (0.6 PSI)/MIN.	EXPLOSIVE RUNS 208 MM. HG (4 PSI)/SEC.
No. of subjects. ....	15	15	No. dizziness. ....	2	1
			% dizziness. ....	6.3	3.4
No. man runs. ....	32	29	No. collapse. ....	2	1
No. bends. ....	13	16	% collapse. ....	6.3	3.4
% bends. ....	40.6	55.2	No. bends & chokes. ....	1	0
No. chokes. ....	5	4	% bends & chokes. ....	3.1	0
% chokes. ....	15.6	13.8	No. dizziness & bends. ....	0	1
No. nausea. ....	3	1	% dizziness & bends. ....	0	3.4
% nausea. ....	9.4	3.4	No descent. ....	3	4
No. gas. ....	3	1	% no descent. ....	9.4	13.8
% gas. ....	6.3	3.4			

respiratory discomfort with successive periods of pressure breathing. It may be well to stress this observation for it is evident that to insure uniform results, the indoctrination in pressure breathing should consist of several periods of pressure breathing in order that the subjects may be thoroughly familiar with and accustomed to the techniques involved. This decrease in the number of descents due to causes other than bends probably contributed to the increased percentage incidence of bends by allowing the subjects to remain at altitude long enough for intolerable bends to develop.

In general, explosive decompression exerted no significant influence on the ability of subjects to tolerate an altitude of 45,00 feet while using pressure breathing.

## DISCUSSION

Paul Bert (3) pointed out more than 70 years ago that changes in barometric pressure have no effect on the tissues of the body provided that these changes are applied to the body as a whole. This is, of course, due to the fact that the body is essentially a liquid system and therefore changes of pressure applied to the body surface are transmitted rapidly and without diminution to all of the internal parts. This fact undoubtedly explains the failure of explosive decompression to produce any marked physiological effects in these experiments. Such effects as were produced were undoubtedly the result of gas expansion in the gas-filled cavities of the body: the gastrointestinal tract, the pulmonary system, the accessory air sinuses and the middle ear. In these regions positive pressures of varying degrees develop and persist until equalization with the ambient atmosphere takes place by the escape of air from the cavity in question.

In our experience, equalization of pressure in the case of the sinuses and middle ear invariably occurs without difficulty, even when the explosive decompression is very rapid. This finding is in agreement with the reports of Armstrong (4) and Sweeney and Joffe (5). Furthermore it is a common observation that difficulty with ears and sinuses is relatively rare when the pressure is being decreased (ascent). Audiographic studies, moreover, indicate that even a series of explosive decompressions, a most unlikely occurrence for the average aviator or air traveler, has no effect on auditory acuity. It is obvious, however, that individuals in whom the openings of the sinuses, or the Eustachian tubes, are occluded for any reason, may suffer ill effects as the result of pressure changes.

Expansion of intestinal gases was commonly noted in these experiments but as a rule did not result in serious discomfort. The incidence of such discomfort was not greater following explosive decompression than in slow ascents to similar altitudes.

Positive pressures in the pulmonary system develop when the ambient pressure falls at a faster rate than that at which the lungs can decompress. The maximum rate at which the lungs can decompress is of course a function of the cross sectional area of the trachea. This positive pressure in the lungs causes an expansion of the thorax which is commonly felt by the subjects. Indeed, Sweeney and Joffe (5) have reported twinges of pain which they attribute to stretching of the attachments of the diaphragm.

Because of the development of pulmonary pathology in animals subjected to more severe explosive decompressions (2), and in view of the report of Barach *et al.* (6) of the development of pulmonary tuberculosis in as-

sociation with exposure to reduced barometric pressures, careful attention was given to examination and x-ray studies of the chests of our subjects. No evidence of pulmonary pathology was found. No follow-up of these subjects has been attempted, but in the four years that have elapsed since the completion of these experiments no news of subsequent development of pulmonary disease in these men has been received by the laboratory.

The results obtained in the experiments designed to determine the effects of explosive decompression on the incidence of incapacitating bends seemed to indicate that explosive decompression at the rates and ranges used in these experiments produces a slight increase in susceptibility to decompression sickness.

While it was only in two groups, *I* and *IV*, that the occurrence of incapacitating bends was significantly greater following explosive decompression than in control runs it is nevertheless true that in the remaining groups there was invariably a slight tendency for bends to occur more frequently following explosive decompression than after control runs. Even though these differences are not statistically significant we feel that we are justified in concluding that explosive decompression does have a real though slight tendency to increase the incidence of bends. This tendency however appears to be masked whenever other bends-producing factors are introduced in the control runs. Thus in *Group II* the use of exercise in the control runs resulted in an increased incidence of bends which tends to cover up the effects of explosive decompression in experimental runs. Similarly in *Group III* the increased altitude markedly increased the occurrence of bends in the control runs and this tended to nullify the effects of explosive decompression in producing bends. We may assume that in persons who are susceptible to bends this condition can be produced by various factors such as exercise, increased altitude and explosive decompression. If, therefore, exercise produces the bends on a subject the effect of explosive decompression on the same subject would be obscured. Thus, in *Group I* where the bends-producing factors in the control runs were negligible, explosive decompression had a marked effect in increasing the incidence of incapacitating bends. On the other hand the introduction of exercise in the control runs of *Group II* had a marked bends-producing effect and therefore the addition of explosive decompression produced no significant increase in the occurrence of this condition.

The results obtained with *Group IV* suggest the importance of the range of the explosive decompression in the production of incapacitating bends. It would seem desirable to investigate further this effect, since such findings are of particular importance in determining the optimal pressure differential between pressurized cabins and ambient atmospheres. The

lack of preoxygenation in *Group V* is apparently another factor in production of bends. It will be recalled that this group of subjects used the Automix and therefore did not get 100 per cent oxygen until after the explosion. They therefore had no period of preoxygenation and as a result the incidence of bends was increased in the control groups. This increase, as in *Group II* and *III*, masked the effect of explosive decompression and therefore we find no significant difference in the occurrence of bends in the control and experimental runs.

In conclusion, therefore, we may say that explosive decompression seems to have a slight but significant effect in increasing the susceptibility to bends. There is however no indication in these experiments that explosive decompression is followed by a sudden burst of nitrogen bubbles in the blood and tissue fluids. Furthermore, it has been demonstrated that explosive decompression does not constitute any significant hazard to the average aviators or air travelers. The average normal human being is well able to tolerate such effects as are produced. It is possible, however, that individuals with pathology of the respiratory or gastrointestinal tracts might find explosive decompression hazardous.

#### SUMMARY

No ill effects were noted in 150 normal human beings subjected to 500 explosive decompressions. Electrocardiograms taken during explosive decompressions showed no significant change and there was no difference between chest x-rays and audiograms taken before and after a series of explosive decompressions. No evidence of bubble formation following explosive decompression was noted. There was a slightly higher incidence of incapacitating bends and chokes following explosive decompression, but this effect is easily masked by other bends-producing factors. Explosive decompression exerted no significant effect on the ability of subjects to tolerate an altitude of 45,000 feet with pressure breathing. It is concluded that explosive decompression, within the rates and ranges used in these experiments, does not constitute a serious hazard to normal human beings.

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# *Oxygen Transport, Circulation and Respiration in Healthy Subjects at Simulated Altitudes of 16,000-18,000 Feet*

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THIS INVESTIGATION was carried out during the war years 1942-1943 as part of a project on anoxemia. It was sponsored by the Office of Scientific Research and Development and a report (1) was made to them on its completion. At that time the data obtained were 'restricted' but they have since been reclassified and seem worthy of publication, especially since anoxemia is a feature of many conditions of disease, often complicates anesthesia and is being widely employed as a test of cardiac function.

The early literature has been reviewed by Van Liere (2) and extensively indexed by Hoff and Fulton (3, 4); the more recent literature has been reviewed by Nims (5). Our experiments were initiated to assess the increased pulse rate found at altitude and in anoxemia; was it evidence of cardiac weakness, as certain early work suggested (2) or an indication of increased circulation like the tachycardia of exercise? Also we wished to extend the work of our predecessors to conditions more exactly simulating those to which aviators would be exposed.

The study consisted of observations of pulse rate, blood pressure, respiration and arterial oxygen saturation; together with ballistocardiograms obtained on 21 subjects. All experiments were conducted inside the low pressure chamber at the University of Pennsylvania. The subjects were first tested at sea level and then at simulated altitude of from 16,000 to 18,000 feet. A final series of tests was made after return to sea level. The results showed that, on the average, cardiac output increased by about the same percentage as the oxygen saturation diminished, so that the amount of oxygen transported to the tissues at altitude approximated the normal in many subjects.

## APPARATUS

The altitude chamber, constructed by the York Company, was a large one, cylindrical in shape. It was 20 feet in length and 8 feet in diameter, so that the 4 people working inside were not crowded.

Oxygen saturation of the arterial blood was estimated by Millikan's oximeter (auto-

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matic adjustment type) (6), applied to one ear under the supervision of the late Dr. Millikan himself. The readings were recorded by a modified Tagliabue Recorder (Type 47006), a 6-point printing recorder driven by a photoelectric galvanometer-amplifier system. This recorder was located on the outside of the chamber so that the team outside was constantly informed of the oxygen saturation of the subjects within. At the beginning of each experiment the oximeter scale was set by having the subject breathe oxygen and taking the value obtained as 100 per cent. This was checked at the end of each experiment by repeating the oxygen inhalation. We planned to discard any result in which the two estimations differed by 6 per cent or more but this never occurred. 'Ear thickness' (6) was checked at frequent intervals during the experiment.

At altitude the valves were kept slightly open and the pumps on at all times so that there was a constant flow of air through the chamber. Evidence secured by a Pauling oxygen meter indicated that the ventilation was sufficient to prevent undue accumulations of oxygen from the expired air of the operators who were inhaling it within the chamber.

The ballistocardiograph, designed by Rawson, was typical of his other vertical instruments (7) except that it was shaped like an airplane pilot's seat, so that the subject sat leaning on a back rest  $12^\circ$  from the vertical with his legs separated and about one half extended. The movement was in the vertical plane and it was amplified by a light beam and mirror system. The natural period of vibration when weighted with 100 pounds of iron bars was 13 per second, with 190 pounds,  $10\frac{1}{2}$  per second. The springs were adjusted so that 280 grams displaced the light spot 1 cm. Both ballistocardiograph and camera were within the altitude chamber.

In measuring the results, because the back of the chair was  $12^\circ$  from the vertical, we might have corrected the vertical dimension of the ballistic waves by dividing by the cosine of  $12^\circ$ . We did not do so because the subjects all held their heads up and the position of the thorax was more nearly vertical than that of the back rest. In addition, this cosine is so nearly unity that the correction is negligible.

When these experiments were performed in 1943, cardiac output was calculated in absolute terms by the area formula (8), but the use of the aortic cross section area in such a formula seems no longer justified. Therefore in recent clinical work (15) this factor has been omitted and the results reported as deviations from the average of healthy persons, as the basal metabolic rate is commonly reported. Normal standards have been estimated on this same basis, first by simple statistical analysis (15) and more recently by more elaborate methods devised by Tanner (16). But in this study the values found could not be referred to the mean of healthy persons, or to a normal standard, because of our lack of data on the circulation of subjects *sitting*, especially with legs separated and knees partly extended. Therefore, although we recalculated all the cardiac outputs mentioned in this study by one of the newer methods with 'A' omitted, throughout this paper we have contented ourselves with reporting the cardiac output found at altitude as a percentage deviation from the value found in the same subject under the same conditions at sea level. The results reported in table 1 give an indication of the relation between the circulation of our *seated* subjects and that of the same persons recumbent and standing.

Respiration was measured by having the subject exhale through a Bohr wet gas meter. The figures given are for rarefied air when the subject was at altitude.

#### EXPERIMENTS

The subjects were all males in good health. Their ages varied from 19 to 49 years. As we were chiefly interested in men of military age, only 3 of

the subjects were over 30. The subjects were either medical or pre-medical students, or members of the faculty, so that they were all familiar with apparatus and experimental procedures. Hemoglobin was estimated in each; it ranged from 86 per cent to 107 per cent of expected normal.

For the 'altitude' experiments two teams of operators were necessary. The authors constituted the inside team. Some practice was necessary before they were able to perform the experiments at altitude under the handicap of being attached to the wall by oxygen tubing, oximeter and telephone wires; the gaps in the tables indicate lapses due to such difficulties. The outside team consisted of Mr. Cochran, who ran the pumps and one of the following: Drs. Schmidt, Hodes, Larabee, Comroe, Snyder or Davis.

The subjects alternately sat in the ballistic chair and on a bench alongside it. After the first subject had sat in the ballistic chair for 15 minutes, blood pressure, volume of respiration and a ballistocardiogram were taken. He was then replaced by the second subject and after a similar rest period the tests were repeated. The chamber was then closed and the 'ascent' began, the final altitude being attained in from 10 to 15 minutes. At about 5000 feet the two operators inside put on oxygen masks and breathed oxygen continuously until the return to sea level. The 2 subjects breathed the rarified air and recorded their sensations, if any, after altitude had been attained, by writing them down.

On arriving at an altitude of 16,000 feet for 15 subjects, and 18,000 feet for 6, the chamber was leveled off and the same series of tests were made on the subject sitting in the chair. He was then succeeded by the second subject who was similarly tested after a 10-minute rest period. One half to three quarters of an hour later both subjects were tested a second time at the same altitude. Descent took about 15 minutes unless it was delayed when the chamber was leveled off or even raised to alleviate pain in the ears or sinuses. Both subjects were tested again at sea level.

## RESULTS

The relation between the circulation of 6 of our subjects sitting in the pilot's seat for 15 minutes at sea level and their cardiac output after 15 minutes rest recumbent and 5 minutes standing is given in table 1. In the seat the average circulation is not significantly different from that found when the subjects stood, about 12 per cent below recumbent values. However, when tested at sea level before ascent the average cardiac output of the 24 subjects *seated* exactly equaled the average normal cardiac output per minute found in the recumbent position. After descent the average cardiac output was 8 per cent lower.

*Changes Found on Reaching Altitude.* The average values found are given in table 2 and the statistics of the changes occurring at altitude are given in table 3. Oximeter readings went below 70 per cent in 5 subjects and remained above 80 per cent in 5. In the rest they lay between 70 and 80 per cent saturation. Changes in blood pressure may be dismissed as small and inconsistent from subject to subject. Respiration increased 32

TABLE 1 DIFFERENCES BETWEEN CARDIAC OUTPUT PER MINUTE OF 6 SUBJECTS WHEN LYING AT REST, WHEN SITTING IN AN AIRPLANE PILOT'S SEAT AND WHEN STANDING

SUBJECT	SITTING % change	STANDING % change
Sch	-21	-21
Sla	-22	-28
M	-3	-6
McM	-4	0
S	0	-7
R	-23	-10
Average	-12	-13

TABLE 2 AVERAGE DATA ON CIRCULATION AND RESPIRATION OF 21 HEALTHY SUBJECTS BEFORE AND AFTER REACHING 16,000 TO 18,000 FEET WITHOUT O<sub>2</sub> AND AFTER RETURN TO SEA LEVEL

	BEFORE ASCENT	ON REACHING ALTITUDE	AT ALTITUDE ½ HR OR LONGER	AFTER RETURN TO SEA LEVEL
Pulse rate (per min.)	77	92	93	72
Syst B P (mm Hg)	116	116	116	105
Diast B P (mm Hg)	73	66	63	68
Respiration (l/m)	9.3	12.1	11.8	9.6
Oximeter (% saturation)	95	75	73	95

TABLE 3 STATISTICS ON CHANGES OF CIRCULATION OCCURRING AT SIMULATED ALTITUDE (16,000-18,000 FT)

	MEAN CHANGE %	STANDARD DEVIATION ABOUT THE MEAN %
Arterial O <sub>2</sub> saturation	-21	±7
Pulse rate	+23	±9
Respiration vol/min	+32	±19
Cardiac output per beat	+14	±0
Cardiac output/min/lb	+39	±16
Oxygen transport	+8	±13

per cent on the average, only one subject failed to increase his respiration at altitude. Acceleration of pulse occurred in every subject and it was accompanied by increased output per beat in all but one. In this individual, tested twice, the output per beat remained almost the same.

Ballistocardiograms remained normal in form at altitude but they often recorded a fine vibration, not present at sea level, which was traced to vibrations in the working air pumps. The amplitude of the ballistocardi-

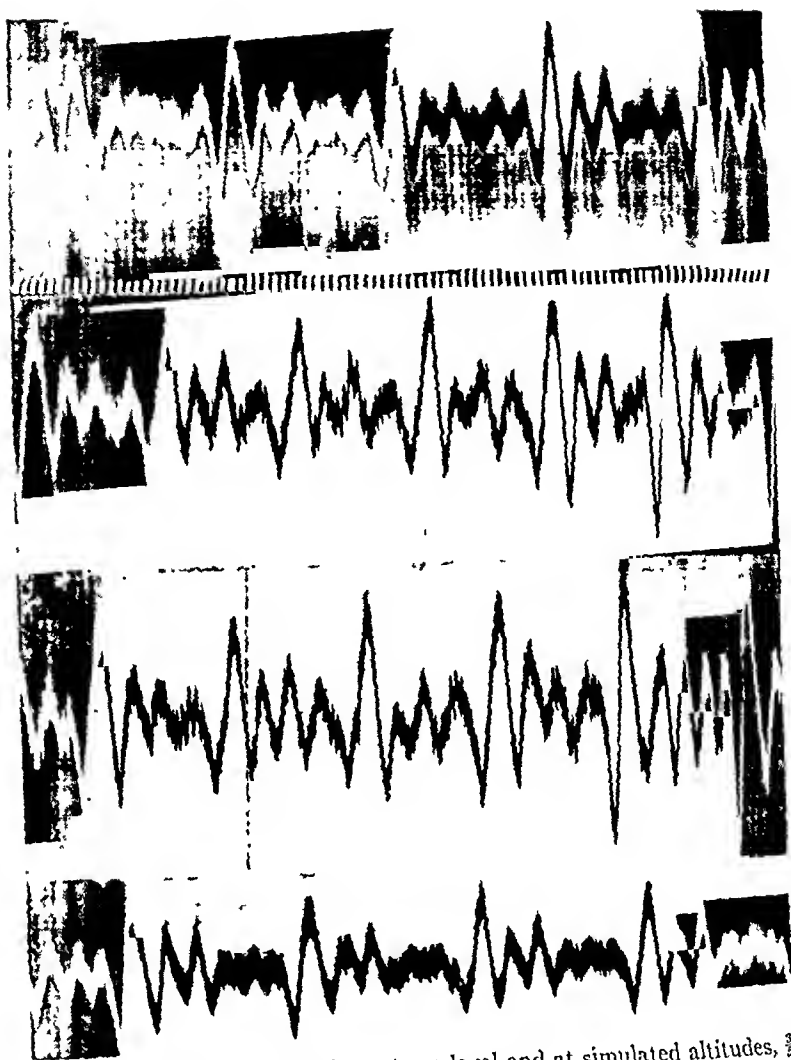


Fig. 1. BALLISTOCARDIOGRAMS taken at sea level and at simulated altitudes,  $\frac{2}{3}$  actual size. The time record at the bottom of the top picture applies to all records, its longest interval is 1 sec. All records were of subject V., age 24, height 5 ft. 8 $\frac{1}{2}$  in., weight 150 lbs., a normal medical student, seated in a pilot's chair.

*Top picture*—11:11 a.m., after 15 min. rest in the chair at sea level. B.P. 132/76; pulse rate 78; cardiac output/min./lb. was 4% above av. normal of reclining subjects; oximeter 95%; respiration 8.3 l/min.

*Second picture*—11:44 a.m., 3 min. after reaching 18,000 ft. (simulated); B.P. 135/70; pulse rate 99; cardiac output/min./lb. had increased 43%; oximeter 72%; respiration 10.7 l/min. Note the fine tremor due to the chamber pumps.

*Third picture*—12:03 p.m. The subject had been at 18,000 ft. for 25 min. He noted slight blurring of vision, felt drowsy and yawned frequently. B.P. 126/60; pulse rate 97; cardiac output/min./lb. was still 43% above the initial value at sea level; oximeter fluctuated between 65 and 73%; respiration 9.4 l/min.

*Bottom picture*—12:52 p.m., 14 minutes after return to sea level. B.P. 120/80; pulse rate 68; cardiac output/min./lb. was 8% below the initial sea level value (4% below the av. normal of reclining subjects); oximeter 93%; respiration 8.1 l/min.

At the beginning of the experiment the oximeter was set at 100% while the subject breathed oxygen. At the end the oximeter read 97.5% while the subject breathed oxygen.

grams was much larger at altitude than at sea level; an example is given in figure 1. The average cardiac output per minute was calculated to be

increased by over one third at altitude. No subject failed to increase his circulation conspicuously. Cardiac output per beat increased less as the average pulse rate increased by only 23 per cent.

*Changes During the Stay at Altitude.* Most subjects had very few sensations although cyanosis was often very marked. The sensations noted were those described under similar conditions (2). The subjects were often conscious of their increased respiration; blurred vision was observed by some but was generally transitory. Sensations such as pins and needles on the skin and warmth of the face or other parts of the body were recorded occasionally; dizziness and weakness were sometimes noted. An occasional subject collapsed but was promptly revived by the administration of oxygen and the rapid descent of the chamber; data on such subjects are not included in this report.

The average oxygen saturation of the arterial blood tended to diminish somewhat with time spent at altitude. This might be explained by the slight diminution of respiration which occurred. The average cardiac output increased during the stay at altitude. This may be thought of as a method of compensation for the increased anoxemia, but the data are also consistent with the view that increased blood flow through the lungs might be a factor in the production of the increased anoxemia.

*Changes After Return to Sea Level.* Except for the respiration, the average values obtained after return to sea level were lower than those found before ascent. This is probably due to the excitement of the experiment passing off. In experiments of many types conducted on the ballistocardiogram at sea level for equivalent periods of time, the final values are often smaller than the initial ones. However, a late effect of anoxemia cannot be positively excluded.

Among the most interesting results of the study are those related to the oxygen transported to the tissues. In order to calculate the change in the oxygen transported to the tissues after reaching altitude, the cardiac output per minute, expressed as percentage of the cardiac output before ascent, has been multiplied by the oxygen saturation, also expressed as percentage of the value before ascent. Results are given in table 4. They show at once that in the great majority of subjects the increase in circulation balances or overcomes the effect of the diminution in oxygen saturation, so that the oxygen transported to the tissues is not diminished at these altitudes.

#### DISCUSSION

Increase in the circulation during anoxemia has been demonstrated by most cardiac output methods employed in the war-time investigations both

in Germany (10) and in this country (2, 5). The chief exception seems to be the data of Motley *et al.* (11) who, using cardiac catheterization, found a diminution of cardiac output after inhaling a gas mixture containing 10 per cent  $O_2$  for 10 minutes. In these experiments the final arterial oxygen saturation was close to that we secured, but the onset of anoxemia was far more abrupt than in our subjects and the exposure was shorter. Keys *et al.*,

TABLE 4. CHANGES IN OXYGEN TRANSPORT TO TISSUES ON PASSING FROM SEA LEVEL TO A SIMULATED ALTITUDE OF 16,000-18,000 FEET AND ON RETURN TO SEA LEVEL

SUBJECT	AGE, YEARS	HB. %	CHANGE IN $O_2$ TRANSPORTED IN % OF 1ST SEA-LEVEL VALUE		
			At Altitude 16,000-18,000 ft.		After Return to Sea Level
			Test 1	Test 2	
Sch.....	49	104	0	-4	+3
Sta.....	47	98	-6		0
H-1.....	27	93	-8	-21	-18
H-2.....	27	93	+6	+10	+9
R.....	26	100	-13		-16
A.....	23	104		-13	-13
T.....	26	94	-4	-5	-12
Ch.....	28	100	+3	-8	-30
K.....	23	100	0	+8	-22
St.....	10	86	+15	+4	+3
Sh.....	24	98	-1	+13	+5
M.....	23		-14	-5	-9
W.....	25		0	+7	-4
V.....	24	98	+8	+2	-8
F.....	23	102	+15	+28	+6
BL.....	28	104	+6	+23	-7
L.....	32	92	-15	-6	
LaM.....	28	92	+8	+28	0
G.....	25	94	-4	+22	-4
D.....	30	96	+4	+12	-14
Wat.....	28		+35	+15	-5
Sn.....	29	97	+43	+14	-7
McM.....	31	89	+40	0	-3
Average.....			+5%	+6%	-7%

(12) who calculated the cardiac output from changes in the x-ray silhouette while his subjects inhaled oxygen mixtures which averaged about 10 per cent  $O_2$ , obtained an average increase of cardiac output of 37 per cent, a figure very close to ours. Steele (13), using a ballistocardiograph for horizontal subjects at simulated altitudes which corresponded to ours, calculated the average cardiac output to increase markedly after altitude. His average is about 5 per cent below our data and the difference may well be due to the difference in position of the subjects. With the head up, the

brain would be more difficult to supply and an increased cardiac output may be needed for this purpose.

We conclude, therefore, that the increased pulse rate found at altitude is analogous to that encountered during exercise and not an indication of cardiac dysfunction from the anoxemia.

Other aspects of our results are worthy of report because our data are so ample. We made many simultaneous measurements on our subjects and so could properly search for relationships by statistical methods. Of especial interest are our data on the oxygen transported to the tissues. After ascent the circulation is increased by an amount sufficient to maintain the oxygen supply to the tissues at a level close to that supplied before ascent.

Recalling the variation of successive ballistocardiograms on the same subject under identical conditions, the standard deviation of the difference is 4.8 per cent of the second estimation, one sees at once that in only 2 of the 21 subjects at the first test and 2 of the 20 in the second test was there a significant lowering of the oxygen transported to their tissues after ascent. In the great majority the oxygen supply was not significantly altered by the ascent. At the bottom of table 4 are placed the results obtained on 3 subjects who increased the oxygen transported to their tissues at altitude. It should be noted that these large increases were not maintained, the circulation tending to subside towards the level needed to maintain the oxygen supply of the tissues at the level present before ascent.

These findings have important physiological implications. Oxygen tension in the arterial end of the capillary cannot be increased by increasing the circulation, but tension in the venous end can be greatly increased if less oxygen is taken out of each unit of blood during its more rapid passage through the tissues. Thus an accelerated circulation benefits subjects at altitude both by maintaining the oxygen supply and increasing the average tension at which it is delivered to the tissues. Doubtless it is this adaptation which permits the maintenance of a normal metabolic rate under conditions of anoxemia (2).

Our experiments had not proceeded very far before it became obvious that 2 subjects exposed to the same rarefied air by no means had identical oxygen saturations in their arterial blood. A comparison between 2 such subjects was possible in 16 instances so we studied that part of the records where the difference was maximal and averaged several simultaneous, or nearly simultaneous readings for each subject; for the 16 pairs the average difference in the oximeter reading between one subject and his fellow in the chamber was 4.4 per cent, the two largest differences were 11 per cent and 10 per cent. When one corrects for the sometimes diverging drift



of the two oximeters by subtracting the differences between the oximeter readings when both subjects breathed oxygen at the end of the experiment, the average difference in oxygen saturation is reduced to 3.8 per cent. This over-corrects the value as the drift was probably a linear function of time and the oximeters started together. The average of the corrected and uncorrected figures, 4.1 per cent is the best estimate for the size of the average difference in oxygen saturation, occurring between 2 subjects breathing the same rarefied air.

The significant differences between 2 subjects were always constant with regard to sign, the more anoxic subject remained so throughout the experiment. Table 5 gives an example which is illustrative although many

TABLE 5. OXIMETER READINGS ON TWO SUBJECTS WITHIN THE SAME CHAMBER

TIME	ALTITUDE	OXIMETER READINGS		REMARKS
		Subject 1	Subject 2	
	ft.	%	%	
11:23	0	100	100	Breathing O <sub>2</sub>
11:24	0	95	95	Breathing air
11:25	0	95	95	"
11:27	3,000	95	95	"
11:32	10,000	92	91	"
11:35	16,000	80	78	"
11:36	"	80	75	"
11:37	"	80	72	"
11:38	"	80	71	"
11:39	"	78	68	"
11:40	"	79	65	"
11:41	"	78	66	"
11:42	"	79	66	"
11:56	"	74	62	"
12:18	0	100	99	Breathing O <sub>2</sub>

more points could have been read from the record. We have given much thought concerning the reasons for these individual differences.

The concentration of oxygen in the alveolar air, which determines the oxygen saturation of the arterial blood, depends in part on the difference between two rates. The respiration pumps oxygen down to the alveolar air, the circulation removes oxygen from it, therefore, if the circulation's uptake were constant, increased respiration should increase the oxygen in the alveolar air and so increase the arterial saturation. Likewise, if respiration were constant, changes in circulation should affect the alveolar air and also the arterial oxygen saturation. We have attempted to see how well these simple conceptions would fit our data.

If subjects at altitude voluntarily hyperventilated, the effect on the

oximeter reading was prompt and striking. All of us could raise our oximeter readings from 5 to 10 per cent—the maximum recorded was 13 per cent—by marked hyperventilation and we learned to relieve annoying symptoms by this means. Needless to say this could not be long continued. But the fact suggested that the differences in the oxygen saturation of individual subjects at the same altitude might be dependent on differences in respiration. Accordingly, we studied our data to find whether the two values were related. However, we found no significant correlation between either absolute volume, or the percentage increase of respiration at altitude, and the arterial oxygen saturation, although the subject having the least diminution of arterial oxygen saturation—88 per cent at 18,000 feet—had the greatest respiration we encountered, 26 l/min.

We also looked for a relationship between the arterial oxygen saturation at altitude and the amount of the circulation, but again we found nothing significant. Finally we estimated the percentage change in respiration on ascent and the percentage change of circulation on ascent, subtracted the second from the first and studied the correlation between this difference and the arterial oxygen saturation. Again the correlation was not significant. Besides the striking transient effect of voluntary hyperventilation, which far exceeded in degree the involuntary increments of respiration found at altitude, our data give no explanation of the individual differences in arterial oxygen saturation found in persons at similar altitudes.

Obviously we are dealing with a complex situation. The volume of respiration in liters per minute is an imperfect indication of the ability of the respiratory mechanism to pump oxygen to the alveoli; it has long been known that rapid shallow breathing is far less effective than deeper breathing. Little is known about the effectiveness of the distribution of blood and air in the lungs during anoxemia, whether some alveoli are better ventilated than others and whether the blood is distributed to best advantage. Factors such as these may well be the explanation of our failure to find correlations with the volume of respiration and circulation which would explain the differences in arterial saturation found in healthy subjects at the same altitude.

However, even without a satisfactory explanation the fact remains that subjects breathing the same concentration of rarefied air may have very different arterial oxygen saturations and the amount of oxygen supplied to their tissues may differ considerably also. This variability must play a part in the scatter of results when anoxemia is used to test cardiac function.

#### SUMMARY

Twenty-one healthy adult subjects were tested at sea level and at simulated altitudes of 16,000 and 18,000 feet in a low pressure chamber.

The subjects sat in a ballistocardiograph built in the shape of an airplane pilot's seat. Blood pressure, respiration and arterial oxygen saturation were measured and cardiac output and pulse rate were estimated from the ballistocardiograms. All these estimations could be made simultaneously or nearly so.

The increase in respiration and pulse rate and the diminution of arterial oxygen saturation at altitude coincided with expectations from previous work. The cardiac output increased by an amount sufficient to transport to the tissues at altitude a supply of oxygen which usually equalled or slightly exceeded that present before ascent.

The arterial oxygen saturation of healthy persons breathing the same rarefied air within the chamber at altitude often differed considerably and we have sought the reason for such differences. Voluntary hyperventilation by any anoxemic subject increased his arterial oxygen saturation considerably, but the long-continued differences in level of arterial oxygen saturation often found between subjects breathing the same rarefied air could not be explained by differences in their total volume of respiration or circulation.

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## *Variations in Venous Pressure under Negative Acceleration*

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NEGATIVE ACCELERATION, as defined by Armstrong (1) forces blood toward the cephalad end of the body, causing an increase in intravascular pressures in the head. By virtue of their anatomy the vessels of the arterial tree are able to withstand great increases in pressure, but this is not true of the thin-walled capillaries and veins. Injury from negative acceleration of several seconds' duration first appears as rupture of small, unsupported capillaries about the head, especially in the conjunctive and upper respiratory mucosa (2). The discomfort, which is one of the limiting factors in human tolerance to negative acceleration, consists of a painful sensation of congestion in the face, and can be duplicated by increasing the venous pressure of the head by means of a tourniquet about the neck or a Valsalva maneuver.

Measurement of the venous pressure in the head under negative acceleration should provide an objective index of the tolerability of negative acceleration, and of the amount of protection afforded by a negative  $g$  protective device. A quantitative understanding of the manner in which venous pressure varies with negative acceleration is necessary in any such study.

Wilkins, using human subjects exposed to  $-1 g$  on a tilt table (3) found that the venous pressure rise cephalad of the heart was that expected from a hydrostatic column based in the right auricle, and that the right auricular pressure appeared to remain constant or increase slightly. Rushmer (4), working with cats exposed to  $-6 g$  on a centrifuge, found the venous pressure to vary as a hydrostatic column based in the region of the heart.

The present work was undertaken to study venous pressure changes in human subjects exposed from  $-\frac{1}{2}$  to  $-3 g$ .

### EXPERIMENTAL STUDY

Young, male human subjects with no history or evidence of cardiovascular disease were used in this study. Accelerations were obtained on

the A.M.C. Human Centrifuge at Wright Field. The magnitude of the acceleration was determined by the use of previously calibrated chart runs, and was checked by calculation from the recorded RPM and the length of the radius of curvature. An adjustable seat was mounted on the centrifuge to which subjects were secured by safety belt and shoulder harness on their sides in the head-out position.

### *Part I*

These experiments were performed to measure accurately the pressures occurring in the head veins of subjects exposed to negative acceleration, and to correlate these pressures with the magnitude of the acceleration. Pressures were measured with a Wetterer-Gauer pressure gauge, a very small



Fig. 1

variable inductance gauge, which was placed in a glass chamber attached directly to a needle inserted in the frontal vein (fig. 1). The system was filled with isotonic saline solution containing 5 mgm. of heparin per cc. and was flushed periodically to minimize clotting. The pressures and the RPM of the centrifuge were recorded photographically.

Subjects were mounted on the centrifuge in a position simulating that assumed in a fighter plane cockpit. The trunk was inclined backward  $10^\circ$  from the direction of acceleration. The heels were level with the buttocks.

Pressures were measured in 4 subjects during consecutive 15-second runs at accelerations ranging from  $\frac{1}{2}$  to 3 negative  $g$ . These pressures were then plotted against acceleration as calculated from the RPM and the distance from the center of rotation of the centrifuge to the gauge. These

data are shown in figure 2. The pressures were found to vary linearly with acceleration as though from a simple hydrostatic column of constant length.

The slope of such a curve in cm. of  $H_2O$  per  $g$  will be equal to the length of this hydrostatic column (4). Correction for the differences in specific gravity of blood and water and for the variation in acceleration along the radius of the centrifuge were neglected here, as they introduce very small changes in the third figure.

The base of such a column would represent the point of constant pressure in the venous system of the subject exposed to negative acceleration. In order to locate this point with reference to the heart, the distance from

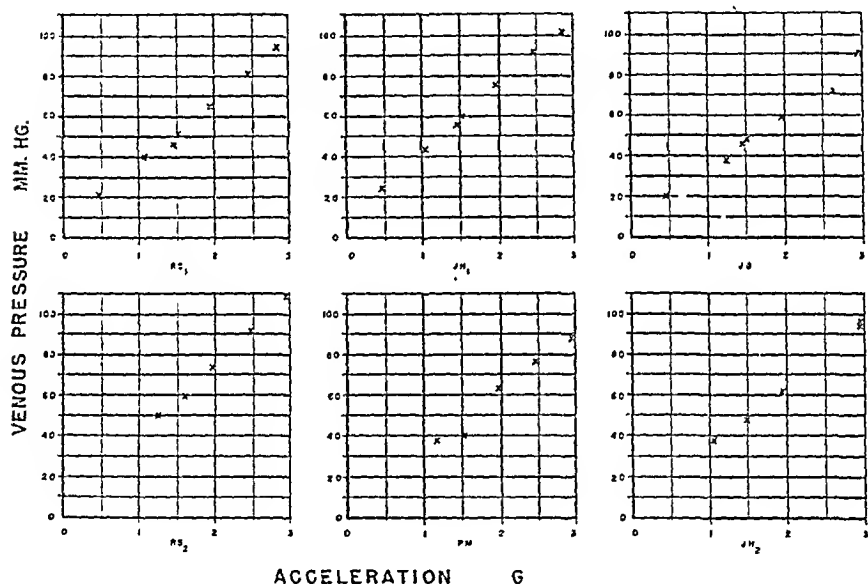


Fig. 2. FRONTAL VEIN PRESSURE versus negative acceleration.

the pressure gauge to the right auricle was determined in each subject. The distance from the gauge to the suprasternal notch was measured and to this was added the distance from the center of the right auricle to the suprasternal notch measured on a P.A. chest plate of the subject exposed to acceleration.

These X-rays were taken on the centrifuge with the subject in the same position as during the pressure measurements. A standard clinical X-ray machine was used with the transformer and control mounted at the center, and the tube mounted on the arm of the centrifuge. Tube distance was 65 inches and the plate was in contact with the anterior surface of the chest. Films were taken of each subject in mid-inspiration at zero, one, two, and three negative  $g$ , and there was found to be essentially no variation in the

position or size of the heart. The center of the diaphragm was found to remain at a constant level while the lateral portions were elevated about one cm. at three *g*. Above 2 *g* there was constantly observed an increased radio-lucency of the basal portions and an increased radio-opacity of the apical portions of the lungs. This is believed to indicate the state of vascular congestion in the lungs.

The computed column lengths and the measured gauge to heart distances are compared in table 1. The base of the calculated column, representing the point of constant pressure in the venous system, was found to lie at or caudal to the right auricle. Duplicate tests on two subjects, *R.S.* and *J.H.*, show that this point of constant pressure not only might lie caudal to the heart but might vary in position in the same subject during different runs. In an effort to explain this inconstancy the experiments in Part II were performed.

TABLE 1. CALCULATED VENOUS COLUMN LENGTHS UNDER NEGATIVE *G* COMPARED WITH DISTANCE FROM GAUGE TO HEART

SUBJECT	CALCULATED COL. LENGTH	GAUGE TO RIGHT AURICLE DISTANCE	GAUGE TO APEX DISTANCE
	cm.	cm.	cm.
<i>R. S.</i>	42.3	38.5	44.5
<i>J. H.</i>	42.2	34.0	40.0
<i>J. G.</i>	33.0	35.5	41.5
<i>R. S.</i>	46.7	38.5	44.5
<i>P. M.</i>	37.4	31.0	37.0
<i>J. H.</i>	41.5	34.0	40.0

## Part II

Experiments were made to determine the effect on venous pressure of the volume of blood contained in the legs of the subject exposed to negative *g*.

Pressures were measured and photographically recorded using a 5 p.s.i. Trimount variable inductance pressure gauge mounted above the subject's brow. The gauge was connected with heavy plastic tubing to a needle inserted in the subject's frontal vein. Gauge, tubing and needle were filled with a heparin-saline solution. A three-way stopcock was inserted in the system to provide for periodical flushing of the needle.

All runs were made at  $-2$  *g*. Two subjects were tested with the thighs and knees flexed  $90^\circ$ . Circulation in the legs was isolated with pneumatic cuffs about the upper thighs inflated to 200 mm. Hg. Venous pressures under negative acceleration were compared with and without the cuffs inflated with the body oriented as follows: trunk parallel to the direction of acceleration, rotated  $45^\circ$  toward the prone, rotated  $45^\circ$  toward the supine.

These data are presented in table 2. While the relative pressures are significant in these experiments, the absolute values are meaningless because of the distance from needle to gauge and the hydrostatic pressure head introduced thereby. The pressure increase upon release of the cuffs is maximal in the 45° prone position where the legs are positioned to allow maximal drainage of blood into the trunk. In the 45° supine position, where some pooling of blood in the legs might be expected since they are below their vascular attachments, there is a slight decrease of venous pressure upon release of the cuffs. It will be noted that there is considerable difference among the venous pressures in these three positions even with the cuffs inflated. This is due to the differences in the heart to face distances and is the subject of another report.

An additional subject was tested to demonstrate the effectiveness of leg positioning alone in preventing reflux of blood from legs to trunk. In

TABLE 2. EFFECT OF LEG BLOOD ON VENOUS PRESSURE IN NEGATIVE ACCELERATION  
Frontal vein pressures (mm. Hg) at negative 2 g

SUBJECT	45° PRONE			ERECT			45° SUPINE		
	With cuff	Without cuff	$\Delta p$	With cuff	Without cuff	$\Delta p$	With cuff	Without cuff	$\Delta p$
J. H.	7	21	+14	32	51	+19	40	36	-4
R. S.	17	32	+15	42	53	+11	45	43	-2
	Thighs flexed	Thighs 90°	$\Delta p$						
J. G.	16	33	+17						

this case the trunk was maintained 45° prone to the direction of acceleration and the venous pressures compared with the thighs flexed so that the heels were level with the buttocks and with the thighs and knees flexed 90°. The pressure changes here are of the same magnitude as those in the cuff experiments (table 2).

As the veins in the cephalad portion of the body are widely dilated from the pressures they contain there should be little pressure drop due to resistance to flow from heart to head, and these pressure changes should reflect changes in right auricular pressure. A sustained rise in right auricular pressure in the order of 15 mm. Hg is unusual in the normal heart.

#### DISCUSSION

Of particular interest in this work is the production of right auricular pressure rises of up to 17 mm. Hg in normal hearts. In similar cuff experiments under one negative g Wilkins observed pressure differences of 10 mm.



Hg (3). Unlike the increased auricular pressures observed during the Valsalva maneuver, this increase represents a real increment in the pressure across the auricular wall since the glottis remains open and intrathoracic pressure, therefore, essentially unchanged.

Such increases in auricular pressure are difficult to produce in normal hearts because of the heart's ability to adapt itself to tremendous variations in venous return, and the great elasticity of the venous reservoir. During exercise in normal human subjects venous pressure in the relaxed arm is reported to rise as much as 50 mm. of water (5), although Landis reports that in dogs right auricular pressure actually falls during exercise (6). Large dosages of sodium chloride may result in great increases in extracellular fluid and blood volume with rises in venous pressure as high as 126 mm. of water (7). In our experiments the rises were in the neighborhood of 200 mm. of water. Constant intravenous infusions in dogs must cause an increase in blood volume of at least 50 per cent before a rise in right auricular pressure occurs (8), and a sustained rise has been noted to appear in only one out of three dogs with tripled blood volume.

Under negative acceleration the trunk of the human subject may receive a massive and sudden 'transfusion' of blood from the lower extremities (about 800 cc. is available (9)). At the same time the subject loses the use of the legs as a pool in which to accommodate sudden increases in blood volume. In addition the bradycardia which regularly appears during negative acceleration interferes with the heart's capacity to increase cardiac output to take care of the increased venous return. Combination of these factors results in the sustained increase of right auricular pressure which was observed in these experiments.

It is possible that an auricular pressure increase did not appear in Rushmer's studies because the cat's hindquarters contain proportionally less blood than do man's, and the legs were flexed, resulting in a smaller percentage increase in the volume of blood in the upper body of the animal exposed to negative acceleration; and consequently less likelihood of exceeding the heart's ability to accommodate all of its venous return. The leg blood is probably often critical in tipping the balance, because in the experiments of Part I, where the legs were positioned so as to avoid spilling blood into the trunk, the point of constant venous pressure in some cases was very close to the right auricle.

#### SUMMARY

Venous pressures were measured in the frontal veins of human subjects exposed from  $-\frac{1}{2}$  to  $-3$  g. In subjects positioned as in the fighter plane cockpit venous pressure in the head increased linearly with acceleration as

though from a hydrostatic column based at or slightly below the heart. At  $-2$  g drainage of blood from the legs into the trunk resulted in an increase of venous pressure up to 16 mm. Hg. This increase is thought to reflect a similar increase in right auricular pressure.

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## *Field Testing of Army Rations*

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A PRIME LESSON OF WORLD WAR II was the necessity for research on a multitude of problems focussed on the soldier, his relation to his weapons and his environment and their mutual interplay. While this was immediately apparent in the air, with man the critical limiting factor in a complex machine, it was not so rapidly appreciated in such mundane things as feeding troops. Though the science of nutrition had made rapid strides, the art of feeding people had scarcely kept pace. Mechanized warfare outmoded the kitchen and group mess for many men in combat. Expeditionary force rations packaged for use by the individual soldier had to be contrived. It is natural that the early ones had shortcomings. Field tests played an important part in their continual improvement, just as with weapons, vehicles, clothing and other appurtenances of war.

This report is concerned with the general principles of organizing and conducting a field test of rations and some observations made during one such test. The results of this and earlier tests have been reported in part in other places but there has been no general discussion of the philosophy of ration tests, the practical problems and ways of meeting them. Had this information been available at the start of World War II the program of feeding soldiers in combat would have been much simpler. The implications of such a study for peace time surveys is of real importance.

Since there was no well established precedent for ration tests in World War II, those of various agencies expressed many attitudes and approaches. Techniques became perfected late in the war so that the best results of many tests were never translated into improvements which reached combat areas. Since the experience of the recent past should be available for a permanent program of testing by the Army, and since the techniques have wide applications in medicine, public health and industry, a general discussion of the methodology of field tests is presented here. The experience of earlier trials (1, 2) was available to those drawing up plans of the test described.

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## CONDITIONS

A number of conditions must be satisfied in any field test of rations for the results to have significance.

a. The responsible test officer must have absolute control of the subjects. Once the test has been authorized no outside agency should alter the program, remove personnel or otherwise interfere. The test must have first priority in all concerns of subject and testing personnel.

b. The testing personnel should not be test subjects and should have no direct responsibility in training or tactical problems. Observers should use the rations under test conditions insofar as it does not interfere with their function as observers. They should have a preliminary period of instruction adequate for complete familiarity with the rations, test methods and procedures.

c. There must be enough subjects for the results to have statistical validity. Subjects should be representative of the larger group for whom the rations are intended.

d. The test must last long enough for the results to be meaningful. It is not possible to determine the merits of a ration for long term use by a short test.

e. There must be complete isolation of subjects from outside sources of food. If several groups are tested on different rations simultaneously there must be complete mutual isolation. Trading of ration components within smaller units must be recorded by individual questionnaires or other means.

f. The test subjects must engage in a program of activity based on conditions for which the rations are designed. While combat with all its implications cannot be reproduced in maneuvers the nearest possible approach should be achieved. Army organization must be employed according to routine practices.

g. The test agency should have no equity in the results of the test—a group developing rations should not test them.

h. Test subjects, their line and non-commissioned officers, should be thoroughly briefed as to the purpose of the test and the necessity of free expressions regarding good and bad features of components tested. Their complete cooperation, essential to the success of any test, depends on the ability of the testing personnel to gain confidence of all subjects and to obtain the assistance of officers in keeping morale high.

i. Information obtained in a test held in the zone of the interior should be validated by making similar studies in theaters of operation as near the front lines as practicable.

j. Provision for implementing the recommendations arising from a test should be established prior to the test.

The aim of a field test of rations must include two major points: The *acceptability* of various components in terms of palatability as well as practical military utility and *adequacy* in terms of performance and health. Since acceptability under field conditions may differ from that in a laboratory or a taste panel for screening, no ration should be standardized for procurement without adequate field testing. Even the most satisfactory field test does not disclose the suitability of a ration for combat. Components which are not acceptable in a field test will not prove acceptable under worse situations.

One of the major difficulties with early types of U. S. Army rations packaged for individual use was the failure to consider their acceptability. This arose from the necessity for procuring available food without prior testing, as well as from the belief that emergency rations would not be used for long periods. There was also the belief of some

nutrition experts that each man's ration must include day by day recommended allowances of vitamins, minerals, fat, protein and carbohydrate. Thus from a combination of expediency, ignorance and good intentions, packaged rations were employed which had a number of serious defects as well as excellent qualities.

#### GENERAL METHODS

There are several methods for obtaining information on *acceptability* of ration constituents. Both qualitative and quantitative data can be used and together they provide mutual checks. In the present test, questionnaires provided exact information on the quantity of each item eaten by each subject at each meal and his rating of its acceptability. Measurement of unused food, such as plate waste and unopened items, was checked against the consumption recorded on questionnaires. After a little experience with a ration, failure to open a component indicated very poor acceptability, while plate waste usually indicated that there was too much of a relatively acceptable item. Hoarding was revealed by showdown inspections. It indicated high acceptability and barter value. Casual remarks overheard by observers highlighted general impressions. Additional checks came from weighing the subjects and from individual clinical and biochemical studies. Thus the acceptability of each component of a ration was established by several methods. Internal verification permitted the methods themselves to be evaluated. Had any serious discrepancy appeared in the data it would have been possible to track it down, correct the method or discard it.

The *adequacy* of rations may be evaluated in terms of military performance, physical fitness, morale, sick rates, a number of biochemical levels and concentrations of nutrients in the body and the medical examination. These include appraisals which are subjective, but which are the basis of clinical nutrition; those which are objective, and within limits, of a quantitative nature. Thus testing the adequacy of rations must include tactical considerations as evaluated by the non-commissioned, line and unit officers and medical considerations determined by those trained in the broad disciplines of modern medical and physiologic sciences, as applied to field testing (table 1).

The manner of fulfilling the conditions outlined and methods for obtaining precise information in a field test constitute the subject of this paper. The actual test known variously as 'Operation Topside', Office of the Quartermaster General Field Test No. 273 and Armored Medical Research Laboratory Project No. 30 was carried out on the Second Battalion, 201st Infantry Regiment during June, July and August 1944 in the Pike National Forest, Colorado.

While many persons and agencies had an equity in the test, and the

TABLE 1

TYPE OF DATA	METHODS	RESPONSIBLE PERSONNEL
I Acceptability of rations	1 Daily questionnaire 2 Issue and waste 3 Summary questionnaire 4 Observer's reports	Test subjects Observers Test subjects Observers
II Physical fitness	1 Battery of tests 2 Opinion of officers	Observers Company line and non-commissioned officers
III Military efficiency of subjects	1 Scored rifle firing 2 Training program 3 Marches	Company officers Company officers Company officers
IV Morale	1 Observation	Company officers, observers
V General Health and nutritional status	1 Routine examination  2 Consultation with battalion surgeon	Panel of medical consultants  Test commanding officer
VI Biochemical balances:		
a. Calories	1 Weight and food data 2 Energy expenditure	Observers Metabolism test section
b. Water	1 Determinations of serum protein and chloride 2 Estimate of intake	Biochemical section Observers
c. Salt	1 Determination of serum and urinary chlorides	Biochemical section
d. Vitamins	1 Determination of vitamins C, B <sub>1</sub> , B <sub>2</sub> , and niacin in the fasting state and after load tests	Biochemical section
VII Weather data	1 Headquarters weather station 2 Company weather station	Test commanding officer Observers
VIII Photographic coverage	Colored and "black and white, still and moving pictures	Signal corps photographers

subject personnel and test organizers came from several branches of the Army and from civilian specialists, complete authority and responsibility was assigned to the Test Commanding Officer. Before the test, advice from experts was utilized and conferences were held to get general agreement regarding methods, procedures, controls and significance of possible results. The advice of statisticians was available throughout.

A preliminary indoctrination period of 5 to 20 days, varying with time of arrival of test personnel at Fort Knox, Kentucky, was devoted to training

in conduct of fitness tests, study of rations, familiarization with the questionnaires and a trial run with C Ration on a battalion in battle training.<sup>3</sup>

#### DESIGN OF TEST

In planning a specific test compromises may be necessary to fit actual circumstances since all desiderata cannot be obtained. Some conditions are absolute and cannot be modified, but any deviation must be recorded so that the results may be interpreted accordingly. The following sections describe the procedures used.

The rations tested were the U. S. Army C, K and 10-in-1 Rations and the Canadian Army Mess Tin Ration. As a control a supplemented U. S. Army Field Ration B was employed (3).

The program of ration periods was designed to resemble a hypothetical tactical situation with three weeks<sup>4</sup> of combat rations, two weeks of support area rations and a final three weeks of combat rations. Hereafter these will be called Period I, Period II and Period III. Testing facilities and personnel permitted processing only one of the six companies each day so the schedule was staggered over six days. Also trucks for convoying subjects, equipment and rations were limited and the program had to be arranged with a view to battalion logistics. Therefore on the sixth day the last company was being tested at Headquarters while the first company processed was in the fifth day of its program. A possible complicating factor might have been a sharp general change in weather while different companies engaged in different activities. No such disturbance occurred.

The schedule is given in table 2. The experimental plan included a control company (*F*) on Supplemented B Ration throughout, another company (*H*) on 10-in-1 Ration throughout and four companies whose schedule was varied so that they could be compared with 1) the control group, 2) other companies on the same ration with either the same or different levels of issue, 3) other companies on different rations and 4) themselves, on the same or different rations at different times. Two companies (*G* and *E*), initially on K Ration, had 10-in-1 and Supplemented B Ration for their respective support area rations. Two companies (*Y* and *G*)

<sup>3</sup> Major L. W. Eichna held classes and practice sessions in conducting the fitness tests. Captain D. M. Bell, R.C.A.M.C. and Captain L. M. Richardson were in charge of ration indoctrination. Major W. F. Ashe, 1st Lieutenant C. E. French and others helped draft final plans for the test. Colonel W. Machle, Major W. B. Bean and Major Ashe conferred with regimental and battalion officers of the 2nd Battalion, 201st Infantry Regiment. Colonel O'Reilly, Regimental Commander, Major Robison, Battalion Commander and others worked out detailed plans for handling troops, equipment and supplies. Majors Robison, Bean and Ashe selected camp sites and set up a program of supply and control.

<sup>4</sup> Because of the extra fitness test (§3) Period I was actually 22 days. This additional test was necessary because of a change in elevation from Camp Carson (6,000 feet) to the test Headquarters (9,000 feet) that introduced a variable which required special consideration.

TABLE 2. SCHEDULE OF RATIOMS AND TESTS

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tested C, 10-in-1 and K; K, 10-in-1 and C in that order, respectively. *X Company*, which tested Canadian Army Mess Tin Ration for three weeks, had two weeks on 10-in-1, one on experimental C Ration, one on K Ration and a week with a choice of C, K, or Mess Tin Rations or components.

For the first three weeks all companies were issued rations at a level approximately isocaloric (4500—5000 cal.). They had more than they wanted to eat so waste provided a check on palatability ratings.

During the last three weeks an attempt was made to restrict the issue to that indicated by the designers in packaging the ration (i.e. 3 boxes of K Rations, 10-in-1 for 10 men instead of 8 and 6 cans of C Ration) one ration per man daily. Identical looking vitamin tablets and placebos were given alternate subjects in *F Company* during this period.

The routine of the typical test day is given in table 3. During the morning five procedures were integrated: 1) weighing all men; 2) biochemical studies which required collection of fasting and load samples of urine and blood specimens from 100 men; 3) a clinical examination; 4) the Harvard Step Test; and 5) the Army Air Forces Test. The Army Ground Forces Test was done in the afternoon. Completing this battery of tests and procedures was accomplished only by careful planning and rigid control of men, keeping groups together; keeping the test on schedule and channeling subjects to the proper station at the right time. Laying out the area with attention to scheduled movement aided the process.

The test demanded rigorous activity, with each of six comparable companies carrying out identical training for identical periods, so that if differences occurred they could be related to the one variable—the rations.

Eighteen officers and 30 enlisted men were assigned on temporary duty to the test by the Quartermaster General. Additional observers, officers and men were assigned by the Surgeon General, the Armored Medical Research Laboratory, the Navy and the Royal Canadian Army Medical Corps. A team of civilian and military medical consultants was organized.<sup>5</sup>

Officers were attached to the Armored Medical Research Laboratory, Ft. Knox, Kentucky, for administration and pay. Enlisted personnel were attached to units of the 201st Infantry Regiment. Mail was delivered through routine regimental channels. Packages were opened in the presence of an officer at Test Headquarters to obviate the smuggling of food. Sick

<sup>5</sup> Headed by Colonel J. B. Youmans this section was composed of Major W. F. Ashe, Major W. B. Bean, Dr. C. B. Chapman, Captain M. Corlette, Captain A. Freedman, Dr. M. Hamburger, Jr., Major R. M. Kark, R.C.A.M.C., Dr. R. H. Kampmier, Dr. A. Mendeloff, Dr. J. M. Ruffin, Dr. W. H. Sebrell, Dr. F. J. Stare and Dr. W. P. Sydenstricker. The chemical test section was directed by Dr. R. E. Johnson. The physical fitness testing program was under the direction of Captain D. M. Bell, R.C.A.M.C., after the first series of tests. The metabolism section was headed by Major Norton-Nelson, Armored Medical Research Laboratory, Ft. Knox, Ky.

call was in accordance with company regulations. Discipline was that of the company. Observers were not concerned with training of test subjects.

Duties of company observers (1 officer and 3 or 4 enlisted men) included: 1) control, distribution, supervision of filling out and collection of questionnaires daily; 2) calculation of individual calorie intake; 3) report on

TABLE 3. TEST DAY SCHEDULE

HOUR	PROGRAM ALL MEN	CHEMISTRY SECTION	STEP TEST	AAP TEST	CLINICAL EXAM.	A G Y TEST		
						As-sembly area	Begin field test	Begin march
0445 0500	Reveille	1, 2, 3 <sup>1</sup> Void & discard						
0500-0530 0630	Weighing	1, 2, 3 Void & collect Give test dose						
0645-0700 0800-0900	Breakfast	1, 2, 3 Bleeding	1	3	1, 2			
0900-1000 1000-1100 1030		1, 2, 3 Urine samples	2 3	4 1	3, 4			
1100-1200 1130-1215 1215-1300 1245 1300 1320 1330 1340 1400 1420 1440 1500	Lunch Rest		4	2				
						1, 2		
							1	
							2	
						3, 4		
							3	
							4	1
								2
								3
								4

<sup>1</sup> The numbers 1, 2, 3 and 4 refer to Platoons.

daily observations; 4) supervision of the daily collection and weighing of left-over food; 5) checking all rations for manufacturer and date of packing; 6) monitoring physical fitness tests and 7) weighing subjects. Observers avoided influencing the answers given by test subjects on questionnaires. No leaves or furloughs were granted during the experiment.

#### METHODS OF COLLECTING DATA

The considerable body of data required an accurate and simple system

of collecting and processing. Since it was imperative that the analysis proceed rapidly, facilities of the Machine Records Unit of the 7th Service Command were enlisted. Questionnaires were designed so that data could be transferred to punch cards with rapidity and ease.

For brevity, speed in filing, to assist in punching cards and to facilitate sampling, a code for numbering test subjects was used. The number consisted of an initial letter and three numerals, the letter indicating the company, the first number indicating the platoon and the other two numerals representing the subject's arbitrary number in the platoon. Example: No. G315 indicated that the subject was in G company, 3rd platoon, and the 15th man in the platoon. To facilitate weighings, and pairing men for the pig-a-back test, men in each platoon were weighed initially, the names arranged according to ascending weights and each subject was given his number on adhesive tape which was kept fastened to his identification tags. Each individual record contained the test subject's number.

A questionnaire was filled out by each subject after each meal each day, except *F Company* on Supplemented B Ration with questionnaires during alternate 10-day cycles. Four categories were noted for each ration item in most questionnaires: 1) meal at which a component was used, 2) rating of acceptability: good, fair or poor, 3) quantity consumed and 4) whether used hot or cold. Since the Supplemented B Ration and the *ro-in-1* Ration required group messing, and it was not feasible in the field to weigh the waste of each item issued to each soldier for each meal, consumption figures were determined for the whole company by deducting total waste from total issue of each item. In addition to the record of quantity from which daily calorie consumption per man and per company were calculated, waste was collected by individual component (plate waste or garbage and unopened units) and deducted from the issue by item. If any considerable discrepancy occurred, a showdown inspection was held. This revealed the degree and type of hoarding. In spite of all efforts, there was an irreducible minimum of food unaccounted for—which may have been eaten and not recorded, waste thrown away or hoarded items hidden too well to be found. The customary Army practice of exchange and swapping was accounted for in the quantity partition of questionnaires. There was some lag between issue and return of unopened cans, though the over-all accuracy was not affected thereby.

The questionnaires were collected daily by observers. The quantity of water consumed, the number of hours slept, number of bowel movements for the 24-hour period and the time required to prepare and eat each meal were recorded. Observers calculated individual caloric intake daily, remarked on general fitness and abnormalities of alimentary physiology, submitted reports on acceptability and condition of items, morale, criticisms,

suggestions, unusual weather and the types of activity which might affect consumption of rations. After each testing period, subjects filled out questionnaires stating their general opinions and comments on the items tested. The summary questionnaire on the initial ration was used after each subsequent period to see how well the likes and dislikes were remembered and how consistent they were. The company officers submitted data throughout the test on physical fitness of their men and a biweekly report giving the scored rifle fire (percentage of hits) in trials before and after the hikes.

The Tabulation Section distributed and collected questionnaires and reports, checking for completeness and accuracy. It also scored fitness tests, transcribed chemical data, checked master forms, kept a daily strength roster by platoon and recorded clinical examination data. Records not processed by the Machine Records Unit were sent to the Armored Medical Research Laboratory for final study. The Machine Records Section punched the information indicated using a separate card for each individual per meal. More than 200,000 cards were used.

#### COMMENT

The 10 conditions laid down in the requirements for a significant field test of rations were satisfied in this test. The official report (9) is available in The Army Field Laboratory giving full details of the results of the test, and specifying how each condition was fulfilled. Subsequent validation of the results in several combat areas was obtained.

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## *An Analysis of Subjectivity in the Clinical Examination in Nutrition*

WILLIAM BENNETT BEAN,<sup>1</sup> *From the Armored Medical Research Laboratory,<sup>2</sup> Ft. Knox, Kentucky*

IN FIELDS WHERE OBSERVED PHENOMENA CAN BE MEASURED to provide verification, the accuracy of physical diagnosis increases. Thus the pathologist has given much assistance to the clinician by supplying evidence against which clinical impressions may be checked. In the realm of human nutrition, such information has been of little help in evaluating early or mild signs. Much of the current opinion concerning the nature and significance of physical signs suspected of having their origin in nutritional disease at its best is purely descriptive and at its worst is fanciful nonsense. It is not the purpose of this paper to enter into a discussion of medical semantics relating to nutrition, but rather to measure the degree of the individual subjective element in nutritional diagnosis based on physical signs and to comment briefly on some of the medical papers bearing on this topic.

There has been little notice of this source of variation in medical sciences. Comment was made by Wertheimer and Hesketh (15) who found differences in the judgments regarding the classification of anthropological types when made independently by two observers. Only limited attention has been given the problem in the vexed field of clinical nutrition. Where an effort has been made to classify children in four categories of nutrition—'excellent, good, fair and poor'—Franzen (7) and Derryberry (6) have reported most erratic results among independent observers. Although the terms lack specificity, one might have anticipated general trends of agreement. Physicians examining the same children not only varied in the numbers placed in each class but frequently one child was placed at least once in every category by different observers. Actually the position of the child on the scale of nutrition ratings appeared to be more a function of the examiner than of anything peculiar to the child. The disconcerting situation has been neglected by many contributors to the contemporary literature on human nutrition. In fact there has arisen a concept of specificity of signs attributed to particular vitamin deficiencies which consist of a hierarchy of phenomena alleged to provide the observer with knowledge of degree, duration and type of deficiency syndrome (8-13, 16) without regard for constitutional fabric, trauma, the multitudinous stimuli of the external environment and finally the innate variation in the observers themselves.

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There have been a number of papers dealing with the non-specificity of various 'diagnostic' lesions and a recent trend away from formulary diagnosis. A critique of the entire problem has been presented by Dann and Darby (5) in an important contribution to the appraisal of nutrition in man. They have emphasized some pitfalls in the clinical examination. A recent paper by Leitner (14) has emphasized the heterogeneous nature of the problems involved. The present report, concerned with a measure of the subjective element, takes the problem a step further by emphasizing the uncertainty in diagnosis of a given explicit finding and the differences of opinion which exist among physicians trained in clinical nutrition in the vital matter of what they see when they examine the same subject. Such differences, while not surprising, should be known so that efforts will be made to reach better agreement. Unless they are recognized and evaluated, some of the descriptive aspect of human nutrition will rest on the quicksands of subjectivity.

There was an opportunity to gain information about the degree of subjectivity in the clinical examination during the course of the ration test described previously (1, 2). The team of medical consultants examined the subjects at the beginning of the test, and at the end of periods I, II and III (1, 2). The first and fourth examination included all subjects, the second and third included the 100 men in each of the six companies who had simultaneous biochemical determinations. A total of 513 men had every physical examination. All 14 examiners were not present at each series of examinations; five participated in only one series but several were present each time.

#### PROCEDURE

A set of criteria, standards and definitions was agreed to before the test and was employed throughout as a guide in recording the findings. This is found in Appendix 1. No interpretation of the observations was added by a consultant who merely recorded what he considered the appropriate finding. It is not implied that all the signs recorded have a fundamental relation to specific food factors or general nutritional status. In the routine examination the subjects were inspected by a team of two physicians, one man examining the eyes, the other the rest of the body. At least three pairs of examiners were at work simultaneously—the subjects were lined up in three equal groups. Every tenth subject was studied by each examiner in turn. No effort was made to keep the same combinations at work together, so the available comparisons differ among the various examiners.

#### RESULTS

The results have been studied by a variety of methods. In the first report (2) averages were treated alone and, since the vast majority of subjects did not have any major disturbances in physical findings, the figures

showed a very good agreement (2, 3). Closer analysis of the data has given a new insight into the problem.

In order to reduce the number of comparisons required and to increase the size of groups compared, all the examinations done in common by one examiner and each other examiner were pooled. Corresponding examinations done by each examiner were treated similarly. By this procedure a comparison could be made of each individual examiner with the average of other observers with whom he examined the same subjects. A  $X^2$  test was made of any differences which appeared between any one examiner and the

TABLE 1. SIGNIFICANT DIFFERENCES FOUND IN THE PHYSICAL EXAMINATION DATA, INDICATED FOR EACH OBSERVER AND VARIOUS SIGNS

OBSERVER	EYE.						MOUTH							SKIN	
	No. of Comparisons	Scleral Opacity	Scleral Vascularization	Pterygia	Conjunctivitis	Pingueculae	No. of Comparisons	Good	Fair	Poor	Cheilosis	Gingivitis	Inflammation of Gum Margins	Follicular Hyperkeratosis	Acneiform Eruption
A	223					M	35	M	L						
B	199	M	M	M			52	L		M					
C	142		L	L	L	L	25	L							
D	82						61				M			M	
E	39					L	0								
F	18						78				L	L			
G	9						137	L	M			M	M	L	L
H	8						105	M		L	L		L	M	M
I	0						36								

M indicates that the observer recorded significantly more ( $P > 0.05$ ) and L significantly less of the particular sign than others examining the same subject.

others with whom he made independent examinations of individual subjects at any given time.  $P > 0.05$  was considered significant.

The general results are presented in table 1. Only examiners with 25 or more comparisons are included. There was no consistency in the individual deviations from the group experience, which indicates at least that the results were really independent. A tendency existed for high and low ratings in any category to counterbalance as would be expected from the method of analysis. Those who departed from the average findings did not regularly find more of each condition under observation, nor did any observer consistently report less. In the case of observers C, E and F the only variation from the comparative base line was in the direction of lower incidence.

Table 2 gives in detail the numerical data on individual performance using the examination of the mouth as an example. There are several cases of wide variation. For instance, the diagnosis of cheilosis by *D*, *F* and *H*

TABLE 2. NUMERICAL DATA ON COMPARISONS BETWEEN EXAMINERS FOR ORAL SIGNS

EXAMINER	CHEILOSI	GINGIVITIS	INFLAMMATION OF DENTAL MARGIN	ORAL HYGIENE			NO OF EXAMS IN COMMON
				Good	Fair	Poor	
<i>A</i>	2	3	2	18 <i>M</i>	11 <i>L</i>	6	35
Others with <i>A</i>	5	3	5	10	20	5	
<i>B</i>	0	9	3	1 <i>L</i>	18	11 <i>M</i>	52
Others with <i>B</i>	0	8	7	8	18	4	
<i>C</i>	2	8	0	2 <i>L</i>	20	4	25
Others with <i>C</i>	2	9	0	10	13	3	
<i>D</i>	16 <i>M</i>	7	6	15	9	7	61
Others with <i>D</i>	3	6	3	16	12	3	
<i>F</i>	0 <i>L</i>	0 <i>L</i>	4	14	35	18	78
Others with <i>F</i>	7	17	5	18	36	13	
<i>G</i>	11	30 <i>M</i>	36 <i>M</i>	29 <i>L</i>	63 <i>M</i>	16	137
Others with <i>G</i>	9	20	12	48	47	15	
<i>H</i>	1 <i>L</i>	17	4 <i>L</i>	30 <i>M</i>	33	4 <i>L</i>	105
Others with <i>H</i>	11	19	27	22	43	11	
<i>I</i>	0	6	3	7	24	5	36
Others with <i>I</i>	0	4	1	4	24	8	

The following significant differences are indicated above by italics

*A*—More good and less fair oral hygiene.

*B*—Less good oral hygiene, more poor oral hygiene

*C*—Less than average good dental hygiene

*D*—More cheilosis.

*F*—Less cheilosis and gingivitis

*G*—More gingivitis, more inflammation of dental margin, less good oral hygiene, more fair oral hygiene

*H*—Less cheilosis, less inflammation of dental margin, more good oral hygiene and less fair oral hygiene

ranged widely. These observers made this diagnosis 5.3 times, 0.1 times and 0 times as frequently as others simultaneously examining the same subjects. With reference to inflammation of the gums at the dental margin there was one examiner who recorded a high incidence and one a low incidence. The



same high and low ratings were noted in the data on gingivitis. Estimation of oral hygiene, depending as it does on much less exact standards of refer-

TABLE 3. AVERAGE AGREEMENT ON ALL FINDINGS, POSITIVE OR NEGATIVE

ABNORMALITY UNDER EXAMINATION		% AGREEMENT
<b>Eyes</b>		
Dryness.....		100
Gross changes in scleral opacity (all degrees of severity).....		78
Gross changes in scleral opacity (moderate and severe).....		92
Gross changes in corneal opacity.....		98
Vascularization.....		92
Gross conjunctivitis (all degrees of severity).....		86
Gross conjunctivitis (moderate and severe).....		96
Pterygia.....		89
Pingueculae.....		95
<b>Skin</b>		
Follicular hyperkeratosis (all degrees of severity).....		81
Follicular hyperkeratosis (moderate and severe).....		96
Acneform eruption (all degrees of severity).....		84
Acneform eruption (moderate and severe).....		98
Dermatitis of riboflavin deficiency.....		100
Petechial hemorrhages.....		100
Purpura.....		100
Pellagrous dermatitis.....		100
<b>Lips &amp; Mouth</b>		
Angular fissures.....		99
Cheilosis.....		92
Pellagrous glossitis (all degrees of severity).....		98
Pellagrous glossitis (moderate and severe).....		100
Pellagrous stomatitis.....		100
Chronic gingivitis.....		99
Active acute inflammation of dental margin.....		87
Good oral hygiene.....		77
<b>Neuromuscular</b>		
Muscular weakness.....		100
Absence of knee jerks.....		99
Absence of ankle jerks.....		99
Tenderness of belly of calf muscle.....		98
Nerve tenderness.....		100
Loss of vibratory sense.....		100
Symmetrical muscular atrophy in extremities.....		100
Pitting edema (pretibial).....		99
Pitting edema (pedal).....		100
Pitting edema (sacral).....		100

ence, was notoriously variable, and only *D*, *F* and *I* failed to show some significant difference from the recordings of the observers who were compared with them.

TABLE 4. CLINICAL DATA AT START OF TEST: POSITIVE OCULAR SIGNS

COMPANY	GROSS CHANGE IN OPACITY OF SCLERA		GROSS CHANGE IN OPACITY OF CORNEA	VASCULARIZATION OF CORNEA, HAND SLIT LAMP	GROSS CONJUNCTIVITIS		PTERYGIA	PINOECULAE
	S	M & S <sup>1</sup>			S	M & S <sup>2</sup>		
E	75	8	3	12	60	12	14	8
F	73	5	1	2	71	7	6	7
G	55	8	0	2	55	12	7	10
H	65	9	0	9	52	17	10	8
X	51	16	0	10	29	10	14	11
Y	38	15	5	17	8	2	7	3

S Slight. M &amp; S Moderate &amp; Severe.

<sup>1</sup> Severe in only 0.3% of total examinations. <sup>2</sup> Severe in only 0.1% of total examinations.

Dryness was reported only once in 2052 examinations.

TABLE 5. CLINICAL DATA AT START OF TEST: POSITIVE ORAL SIGNS

COMPANY	ANGULAR FISSURE	CHEILOSI	(RED) GLOSSITIS OF PELLAGRA	GINGIVITIS	ACTIVE ACUTE INFLAMMATION OF DENTAL MARGIN	ORAL HYGIENE		
						Good	Fair	Poor
E	0	15	2 <sup>1</sup>	32	36	28	55	17
F	0	2	0	11	20	46	43	11
G	0	5	0	20	19	45	47	8
H	0	8	0	20	15	59	35	9
X	0	3	0	15	3	49	49	2
Y	2	5	0	12	4	34	55	11

<sup>1</sup> Slight. Pellagrous stomatitis—none seen.

TABLE 6. CLINICAL DATA AT START OF TEST: POSITIVE DERMAL SIGNS

COMPANY	FOLLICULAR HYPERKERATOSIS		ACNEFORM ERUPTION		PETECHIAL HEMORRHAGES	PELLAGROUS DERMATITIS				
	Slight	Mod. & Sev. <sup>1</sup>	Slight	Mod. & Sev. <sup>2</sup>		Ac.	Chr.	Sl.	Mod.	Sev.
E	26	4	20	5	0	0	0	0	0	0
F	34	2	16	2	0	0	1	1	0	0
G	30	1	33	5	0	0	0	0	0	0
H	29	3	14	1	0	0	0	1	0	0
X	19	1	10	2	1	0	1	1	0	0
Y	13	2	17	4	0	0	0	3	0	0

<sup>1</sup> Severe in only 0.2%. <sup>2</sup> 1 severe case in 2052 examinations.

Dermatitis of riboflavin deficiency; purpura—none.

Data from examination of the eyes and of the skin (table 1) reveal similar but much less frequent divergences from the common experience.

found in the observations by a group of physicians trained in clinical nutrition and using a set of objective standards when they examined soldiers for signs possibly indicative of nutritional deficiency. In some cases patterns of performance were noted. Several physicians had a tendency to find particular signs with unusual frequency or unusual rarity.

These observations underscore an uncertainty in the clinical evaluation of nutrition and emphasize the inexactness of clinical data dealing with signs of deficiency diseases. These conclusions do not apply to advanced states of deficiency syndromes where agreement may be unanimous.

*Appendix. CRITERIA, STANDARDS, AND DEFINITIONS OF PHYSICAL FINDINGS FOR USE IN EXAMINATIONS FOR NUTRITIONAL STATUS*

*a. Vitamin A*

1) Eyes—Lack of tearing; dryness of conjunctivae and sclerae.

Conjunctivitis—Characterized by the usual signs of inflammation—redness, injection and swelling; graded *slight*, *moderate* or *severe*. *Slight* means redness and injection of conjunctivae with little or no swelling or photophobia and minimal involvement of the bulbar conjunctivae (sclerae). *Moderate* is of greater extent with some photophobia. *Severe* includes swelling blepharospasm. Degree of lachrymation is significant in relation to conjunctivitis as is photophobia. Purulent conjunctivitis to be noted.

Local or general thickening of sclera characterized by loss of translucency, loss of sheen, elevation and pigmentation; graded *slight*, *moderate* or *severe*. *Slight* to be interpreted as one localized area in either eye or diffuse thickening of significant grade according to judgment of examiner; *moderate*, 2 to 4 localized areas without significant elevation or pigmentation, or moderate diffuse thickening; *severe*, characteristic Bitot's spots and/or gross diffuse thickening folds. Note pterygia and pingueculae.

Cloudiness or steamininess of cornea, localized or general, otherwise unexplained. Recorded merely as involvement of cornea.

2) Skin—

a) Follicular hyperkeratosis consisting of at least several grouped papules, present in at least one of the sites of predilection (the lateral surfaces of arms, thighs, and lower abdomen) as well as in any other location, without any consistent folliculitis (infection). Other features considered in forming clinical judgment are dryness of the skin, degree of sweating relative to environment and broken hairs. Graded *slight*, if papules small and confined to approximately one third of thighs, arms or abdomen; *moderate*, if papules larger, even though confined to any two of above sites; *severe*, if papules large (25 mm.) and involve above and additional areas.

b) An acneform eruption consisting of numerous (more than 3-4) red papules simulating acne but with little actual infection (pus), distributed over trunk and arms with little or no involvement of face. Graded *slight* if not more than six, or if confined to back, chest, or arms; *moderate*, if 10 to 20 or involving two or more of above areas; *severe*, if in greater number in all areas.

*b. Vitamin B<sub>1</sub> (Thiamine)*

- 1) Muscular weakness, lower extremities. Determined during physical fitness tests.
- 2) Muscle tenderness (bilateral). Determined by pinching belly of gastrocnemius with force adjudged by examiners not to cause pain in normal subjects and graded *slight*, *moderate* or *severe* according to judgment of examiner.
- 3) Nerve tenderness (bilateral). Determined by pressure over peroneal nerve at head of

fibula with force adjudged by examiner not to cause pain in normal subject. Distinction to be made from paraesthesia. Graded *slight, moderate, or severe* according to judgment of examiner.

- 4) Loss of vibratory sense (bilateral). Tested over internal malleolus with tuning fork (256). Recorded *present or absent*.
- 5) Loss of reflexes (bilateral). Ankle and knee (patellar) reflexes tested sitting and kneeling without reinforcement. Recorded *present or absent* for each site.
- 6) Muscle atrophy (bilateral). Atrophy of muscles of lower extremity (thigh and leg) otherwise unexplained. Presence of atrophy and absence of other cause determined by judgment of examiner.

of sacrum and legs (shins) and feet determined by palpable examiner. Recorded *present*

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slit lamp (hand or large)  
ea in at least 3 quadrants of  
of vessels to contain blood.  
nd extends nearly to pupil;

rehead) and ears clinically  
r without large, dry come-

n the absence of false teeth

er of lips, with or without  
pes, etc. Recorded *present*

hands, feet, neck or face,  
ion of chronic inflammatory  
squamation and pigmenta-  
*moderate, or severe* by extent

phy of papillae involving at  
luding no more than tip and  
eater in extent or degree or  
m, edema, etc.  
ompanied by glossitis. Re-

in judgment of examiner  
etc.; *moderate*, if more exten-  
sions in mucous membrane

- a) Acute redness and inflammation of dental margin, with or without swelling of interdental papillae, with or without bleeding, spontaneous or on slight trauma.

b) Chronic thickening, lividity and retraction of gums.

c) A combination of both.

Also recorded: the presence or absence of deposits of tartar, cervical fillings, dental work and infection in such relation to the above charges as to possibly account for the occurrence. The latter recorded as *present* or *absent* without particular designation.

3) Muscle tenderness (See Thiamine).

4) Edema (See Thiamine).

#### f. Protein

1) Edema (See Thiamine).

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*Clinical Experience with Hemoglobin-Saline Solutions<sup>1</sup>*

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THE ATTENTION OF THIS LABORATORY has for some years been directed to studies of the behavior of dissolved hemoglobin in the blood stream of man and mammals (1-6). In common with other investigators we have hoped to find therapeutic uses for hemoglobin and particularly for its saline solutions. During the war we made an effort to produce such solutions and we were able to secure a few clinical observations (6). These observations were fragmentary and did not certainly establish therapeutic value for our solutions. However, in some cases there were favorable indications and in a few patients results of physiological importance were obtained. The present communication covers such of these experiences as seem to us to be of interest to other workers in this field. Detailed case reports will not be given, but will be furnished to any reader interested in having more complete information about our patients.

Clinical experience with intravenous injections of hemoglobin solutions begins with the papers of Sellards and Minot (7). These authors were mainly interested in the 'tolerance to hemoglobin' defined as "the amount of hemoglobin required to produce hemoglobinuria". In no case did they observe hematopoietic stimulation by the injected hemoglobin, prepared in sterile solutions, although they made the requisite blood cell studies. The more recent clinical literature has been reviewed by Cannan and Redish (8). They have prepared and injected crystalline human hemoglobin into a series of human subjects. Other important papers are those of Duesberg (9), Ottenberg and Fox (10), O'Shaughnessy *et al.* (11), Fairley (12), Gilligan *et al.* (13) and Kark and Meiklejohn (14). The effects of hemoglobin free in plasma may also be studied in the literature concerning march hemoglobinuria, reviewed by Gilligan and Blumgart (15) and further described by Gilligan *et al.* (16).

None of these reports establishes a therapeutic value for intravenously injected hemo-

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globin-saline solutions. The studies were intended to explore the feasibility of intravenous injections and to determine the maximum safe level (8, 11), to follow the intensity and duration of hemoglobinemia and hemoglobinuria (10, 13, 15) or to search for the appearance of hemoglobin derivatives such as hematin, methemalbumin, porphyrin and bilirubin (9, 12, 13, 14, 16). None of the authors has studied the blood cell picture, hence no observations are reported on hematopoietic stimulation. In nearly all cases only a single injection was made. The maximum amount of hemoglobin administered was about 50 gm. (8, 11); three of the groups did not exceed 10 gm. (10, 12, 13). Most of the authors comment upon the absence of jaundice in their cases. Even the maximum amounts did not produce clinical icterus, although moderate increases in plasma bilirubin were detected (9, 13, 15, 16). Most authors observed no reactions. Reactions occurred for some when the amount injected exceeded 10 gm. (8, 11, 12); nausea, vomiting, tightness of the chest, pains in back and loins and moderate fever are mentioned as symptoms.

It was our purpose to determine clinically the effect of repeated intravenous injections of hemoglobin-saline solutions prepared in this laboratory. We hoped to study the effect of such solutions upon hematopoiesis and in shock. Injections were made into a total of 14 patients. Seven patients were treated repeatedly. Five of these had secondary anemias due to hemorrhage or infection. Two had anemias caused by leukemia and agnogenic myeloid metaplasia respectively. In order to study other phenomena, single injections were given to 7 other patients whose blood pictures were within normal limits.

#### METHODS

*Preparation of Solutions.* In a previous communication (5) we have described our efforts to prepare desiccated hemoglobin in lyophile form. We were never able to produce a dry product which did not contain appreciable amounts of methemoglobin (5-15 %) upon resolution, and which did not show an insoluble residuc. We early observed that the removal of oxygen before freezing and drying diminished the percentage of methemoglobin in our lyophile product, and later found that hemoglobin may be preserved in solution, without formation of methemoglobin or insoluble material, if the oxygen has been removed (17, 18).

We therefore came to work entirely with sterile solutions of human hemoglobin, either freshly prepared, most of the oxygen removed, and refrigerated until used, or sealed in completely oxygen-free ampoules and held at room temperature. In all but one of our clinical tests we have used relatively fresh refrigerated solutions. Many animal experiments have been successfully performed with oxygen-free solutions held for weeks or months. Further clinical experience with solutions of the latter type is needed.

Our solutions were obtained by the use of human red cells, thrice washed with 1.5 per cent NaCl and centrifuged to remove plasma. A sterile technic was followed throughout. To one volume of packed cells we added half a volume of sterile distilled water. To each 100 cc. of the resulting mixture 20

cc. of ether or toluene was added, producing complete hemolysis and formation of a thick gel. The gel was broken by vigorous stirring and centrifuged until it separated into an upper layer containing the precipitated stromata, and a lower layer consisting of clear aqueous hemoglobin-saline, in which pigment concentration ran from 12 to 18 per cent. This clear layer was siphoned off and filtered. The potassium and traces of the organic solvent were then removed by 2-stage dialysis against 1.0 per cent NaCl solution. As a final precaution the solutions were passed through sterilizing filtration. At the same time the oxygen was removed. The solutions were filtered into plasma-vacs, or, alternatively, were led into sterile evacuated ampoules and sealed in vacuo. Samples of each run were rabbit-tested for pyrogens, a limit of tolerance of 1.5°F. rise/10 cc/kg. injected being accepted.

The blood group employed does not influence the clinical results, at least in so far as the major groups (A, B, AB and O) are concerned. In no case have the red cells of our patients been agglutinated by our solutions. Final hemoglobin concentrations were between 10 and 14 per cent. Methemoglobin formed 2 per cent of total pigment.

*Analytical Methods.* Hemoglobin and methemoglobin were determined by the method of Evelyn and Malloy (19). Hematocrits were read by the use of Wintrobe tubes. Reticulocytes were counted by the method of Wintrobe (20). NPN was read by the method of Folin and Wu (21). BUN and urea clearances were determined by the method of Peters and Van Slyke (22). Hippuric acid was determined by the method of Quick (23). Plasma proteins were read by the falling drop method of Barbour and Hamilton (24). Glomerular filtration rate was measured by the mannitol method of Smith, Finkelstein and Smith (25). Renal blood flow and Tm were read by the method of Goldring *et al.* (26), substituting sodium paramino-hippurate for diodrast. Blood and urinary pH was determined by the glass electrode.

#### OBSERVATIONS

*Changes in Blood Pressure, Heart Rate and Temperature after Hemoglobin-saline Injections.* In animals large injections of hemoglobin-saline tend to raise the blood pressure (2) even when the volumes of blood withdrawn, and of fluid injected, are exactly the same. This pressor action may be ascribed in part to the high colloidal osmotic pressure of hemoglobin-saline solutions, which draw fluid into the blood and so raise its volume. A chemical pressor principle is also present.

In our human patients we usually observed an elevation of blood pressure, even after the infusion of volumes of fluid so small that they could not significantly increase blood volume. There were wide individual differences, as shown in figure 1. Patients E. R. and K. K. showed rather small elevations in blood pressure. Patient E. P. was hypertensive. In this case the blood pressure fell after the infusion. The pressor response was well developed in patients H. C., C. H., L. T. and S. L. It was also prominent in M. B. (fig. 2) and M. S.



(fig. 6). . Associated with the pressor rise the heart rate was always diminished, presumably as the result of carotid sinus reflex action.

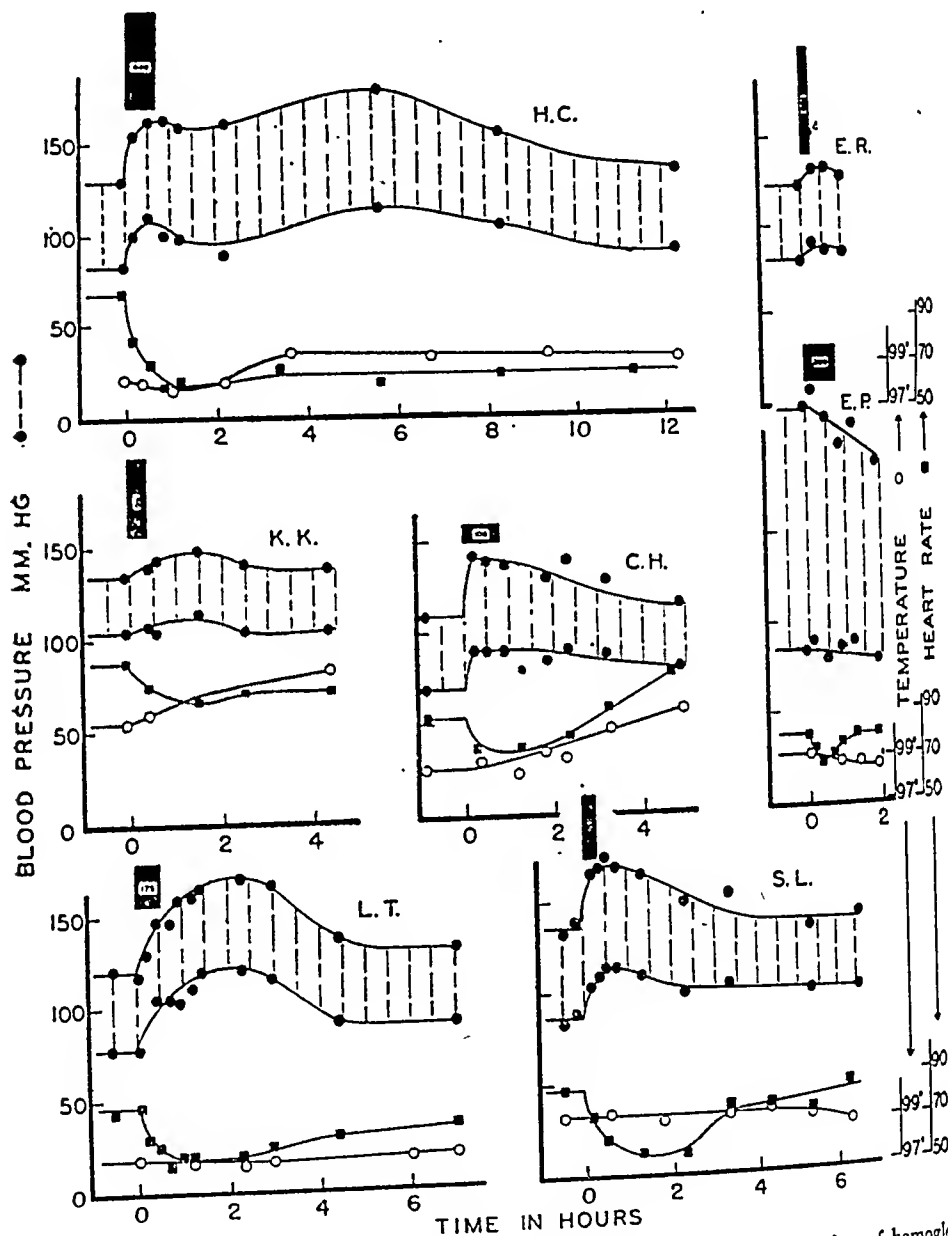


Fig. 1. BLOOD PRESSURES, HEART RATES AND TEMPERATURES after the infusion of hemoglobin into seven patients.

Oral temperatures are shown in the figures. They showed no significant changes in patients H. C., L. T., S. L. and M. B., indicating an absence of pyrogens. In one case, M. B., the injection of a volume as large as 500 cc. gave temperature rise (fig. 2). In other cases pyrogenic reactions were observed usually moderate, but occasionally severe. The observations encourage

belief that, with greater precautions in the preparations of the solutions, it may be possible to produce hemoglobin-saline which will give little or no pyrogenic reaction in any patient.

*Relation between Injected and Excreted Hemoglobin.* The appearance of hemoglobin in the urine, after its intravenous injection, has often been reported and used as an argument against its clinical application. In our cases the hemoglobin recovered in the urine rarely exceeded 25 per cent of that injected and was often much less. Figure 3 shows the relationship between injected

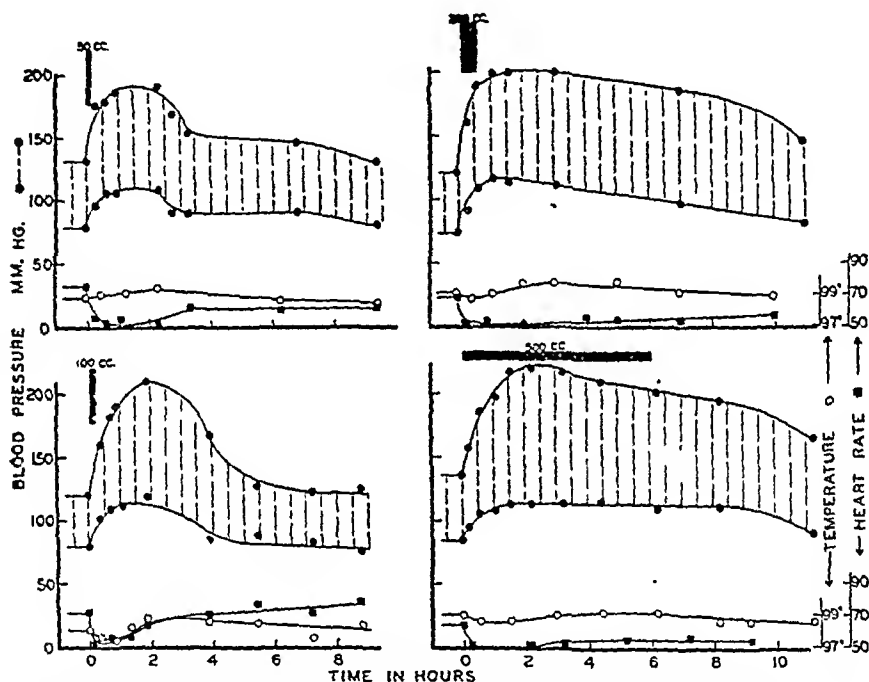


Fig. 2. EFFECT OF INFUSION VOLUME upon the blood pressure, heart rate and temperature in patient M. B.

and excreted hemoglobin in patient H. C. Of a total of 63 gm. injected in this test, only 7.4 gm. appeared in the urine during the next 30 hours, an excretion ratio of 12 per cent. Figure 3 also shows the time course of a moderate diuresis following the injection. In association with this diuresis urinary pH swung toward the alkaline side, then became more acid again as the urine flow diminished. No alkali was given to this patient. In other patients, similar alkaline tides in the urine were detected after hemoglobin-saline injections, even when no alkali was given.

In figure 4 is shown the relationship between injected and excreted hemoglobin in 6 patients. The data include 27 tests, in which a total of 935 gm. of

hemoglobin were injected. Of this amount 167 gm. appeared in the urine, an average urinary loss of 18 per cent. Only in *patient M. B.* did the excretion percentage depart markedly from this average, when the average urinary loss was 41 per cent.

No significant effect of the administration of alkali on the quantity of hemoglobin excreted through the kidney was observed.

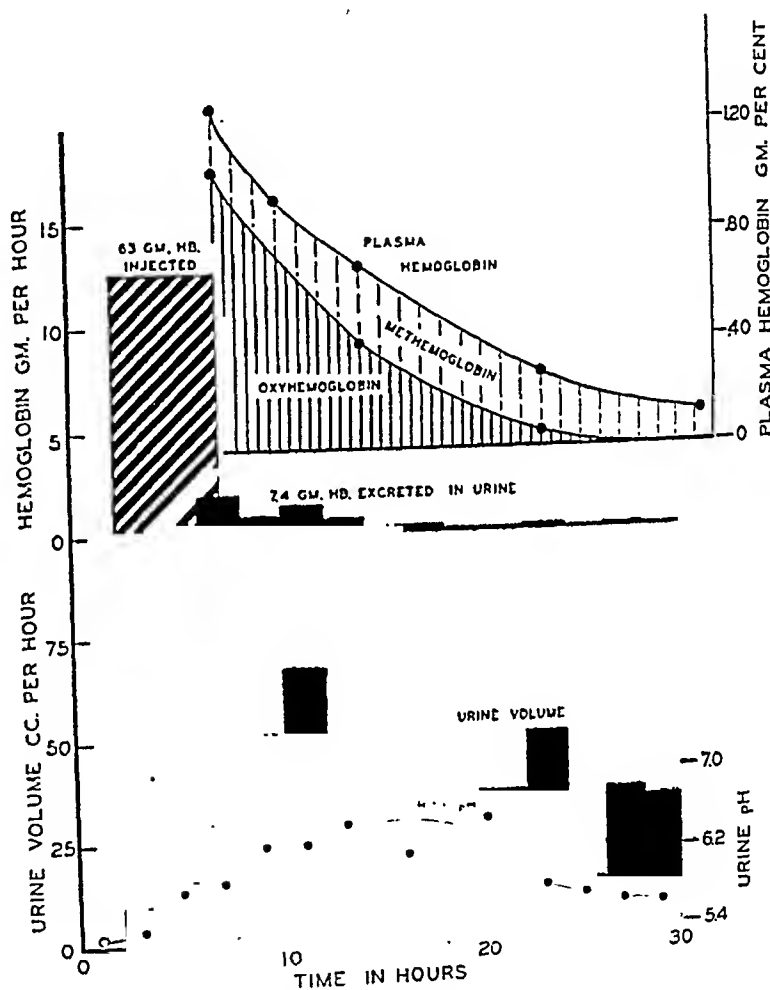


Fig. 3. BLOOD AND URINE CHANGES after injection of 550 cc. of 11 per cent hemoglobin-saline in patient H. C.

*Stimulation of Hematopoiesis.* In three of our five cases of secondary anemia we obtained evidence that intravenously injected dissolved hemoglobin can stimulate hematopoiesis. *Patient L. T.* was a 37-year-old colored female with lymphogranuloma and rectal stricture associated with bleeding which had caused a moderate anemia. *Patient H. C.* was a 35-year-old white female admitted for a chronic osteomyelitis of the left foot, and cellulitis of the lower left leg. A moderately severe anemia was present. *Patient E. R.* was a 34-year-old white male with multiple pyogenic cutaneous ulcers. He had bled

severely as a result of wide excision of these ulcers, his hematocrit finally falling to 18.

In all three cases the repeated intravenous administration of hemoglobin-saline solutions was shortly followed by rises in hemoglobin and hematocrit values. The results of treatment are shown in figure 5. The solution volumes are marked above the arrows which indicate injection times. In patients *H. C.* and *E. R.* hemoglobin and hematocrit values rose together. There was no

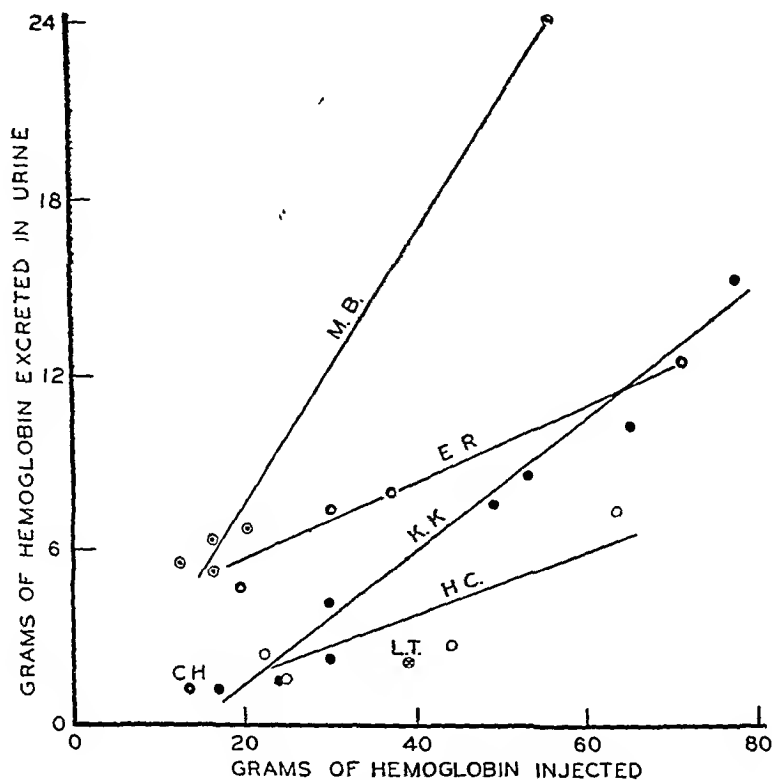


Fig. 4. RELATIONSHIP BETWEEN INJECTED AND EXCRETED HEMOGLOBIN in 6 patients.

significant change in the mean corpuscular hemoglobin concentration. The hematopoietic activity consisted in an accelerated production of more red cells with hemoglobin content similar to those already circulating. Reticulocytes increased in patient *H. C.*, but were very high initially in patient *E. R.* and fell as hematopoietic activity relieved the anemia.

In patient *L. T.* the data were complicated by continuing rectal bleeding, augmented by additional blood loss during and following the first stage of the Lahey operation. Nevertheless the rises in hemoglobin and hematocrit values prior to operation appear to be significantly related to the first series of infu-

sions. Less clearly the later rise in these values may be associated with the smaller second series of infusions. In both series reticulocytes significantly increased. However, an increase in the hematocrit did not keep pace with the rise in hemoglobin. As a result, mean corpuscular hemoglobin concentration,

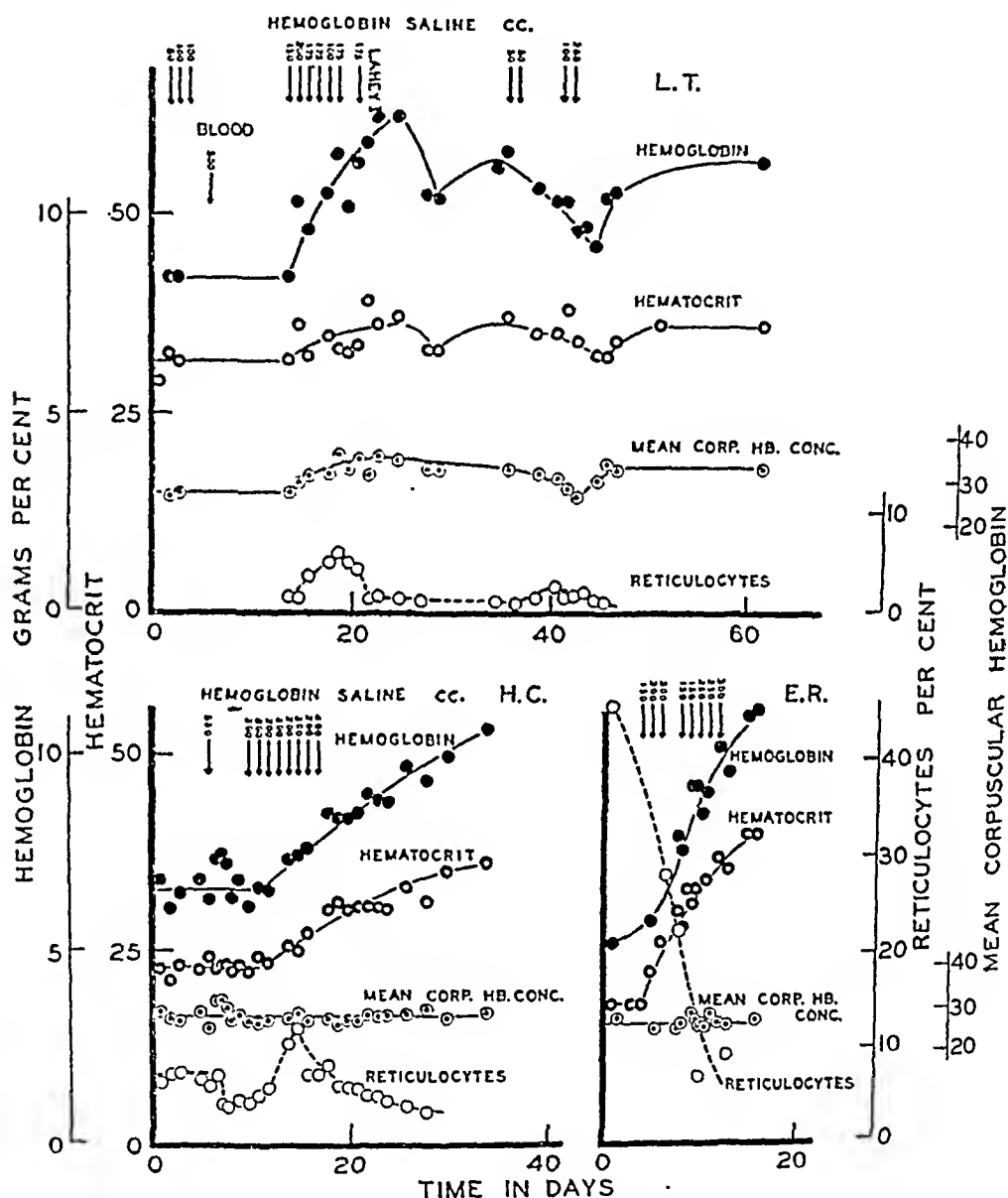


Fig. 5. STIMULATION OF HEMATOPOIESIS by hemoglobin-saline solutions in three patients.

originally low, showed a significant rise. In *patient H. C.* faint icterus was present after the infusions. In all other cases icterus was not observed.

*Treatment of Shock.* It was our original intention to develop hemoglobin-saline solution for use as a blood substitute in lieu of the conventional plasma preparations. The ability of these solutions to transport oxygen seemed to confer upon them an advantage not found in any other blood substitute and to

fit them uniquely for the treatment of shock and hemorrhage. We found it difficult to obtain suitable cases for the study and have treated only a single patient.

*Patient M. S.* was a 22-year-old white female. In her second pregnancy she was admitted on February 2, 1943, for hypertension, but was discharged on February 10, undelivered and improved. She was readmitted on February 17 in active labor. Her blood pressure was 170/110; otherwise her condition was satisfactory. Labor progressed under nembutal and paraldehyde sedation. At 6:50 A.M., February 19, the patient delivered spontaneously a full-term child. The secundines were apparently fully expressed, followed by several blood clots. There was evidence of considerable retro-placental hemorrhage prior to delivery.

The patient was placed in charge of a nurse who was instructed to massage the uterus. The nurse was inexperienced, misunderstood her instructions and left the patient. When next seen by the doctor at 7:45 A.M. the patient had suffered massive hemorrhage and was in a state of collapse. The pulse was not palpable. She was still under the influence of sedation. She was immediately given 500 cc. of plasma, which restored blood pressure sufficiently to permit a systolic reading of 80 mm. Hg. Another 500 cc. of plasma were given at 8:15 A.M. At 9:00 A.M. she received 200 cc. of 25 per cent glucose. Between 9:15 and 10:15 A.M. she received 300 cc. of whole blood—all of her type then available in the hospital bank. These later infusions failed to raise the blood pressure further. The pulse remained rapid (130 to 140) and very weak. Bleeding continued and her condition was critical.

Since no more compatible whole blood was available, the resident obstetrician called one of us (C. M. R.) into consultation and asked that hemoglobin-saline be administered. The cardio-vascular data secured before and after treatment are shown in figure 6. A blood sample, hereafter referred to as the 'control sample', was secured just before infusion began. Beginning at 10:33 A.M. hemoglobin-saline was given into the external jugular vein at the rate of 30 cc/min. until 300 cc. had passed. The blood pressure rose to 106/80 and the pulse dropped to 100 at 10:45 A.M. Consciousness returned at about the same time.

Administration of hemoglobin-saline continued at a slower rate until 500 cc. had been given at 11:00 A.M. At this time the blood pressure was 140/80, pulse 96. Since bleeding continued, the patient was returned to the delivery room for inspection. A small vaginal laceration was repaired and relaxed uterus packed. The uterine cavity was not inspected at this time. In spite of continuing hemorrhage the patient's color, previously ashen, was now good, the pulse volume was greatly improved and the veins were fairly full.

Further infusions of hemoglobin-saline were now given, as shown in figure 6. The final total administered was approximately 2300 cc., containing 250 gm. of hemoglobin. Bleeding continued until mid-afternoon when uterine examination revealed a fragment of retained secundine which was removed. Many clots and much fluid blood were lost at this time, but bleeding then ceased. A severe pyrogenic reaction occurred whose time course is shown in figure 6.

During and soon after the hemoglobin-saline injections a total of 15 gm.  $\text{NaHCO}_3$  were administered. The urine, originally acid at  $\text{pH}$  6.15, turned alkaline about midnight. The  $\text{pH}$  rose progressively throughout the whole course of the case, until a terminal value of 8.9 was obtained although no more alkali was given. To combat both the reactions and the anemia, oxygen was administered almost constantly.

The time course of the changes in plasma and red cell hemoglobin is shown in figure 7. Plasma hemoglobin reached a value of 2.7 gm. per cent immediately after the fourth injection. Plasma proteins were 4.28 gm. per cent in the control blood sample, then rose to values

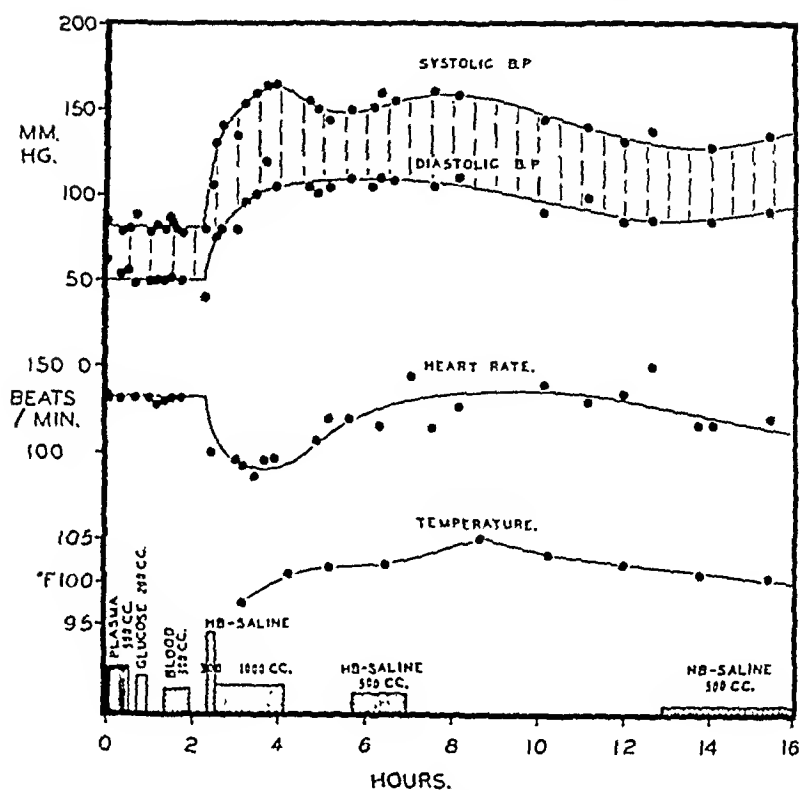


Fig. 6. EFFECT OF HEMOGLOBIN-SALINE in shock—patient *M. S.*

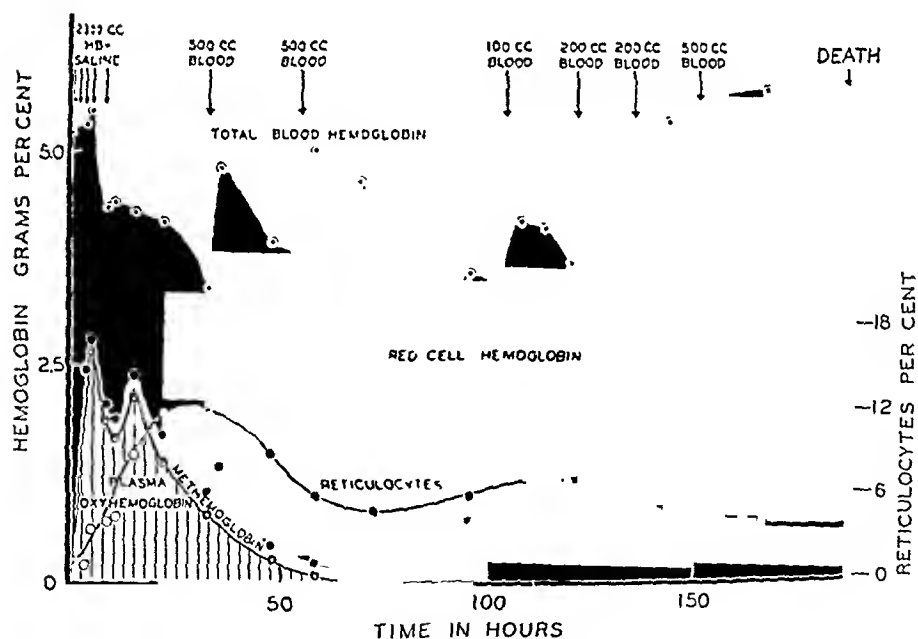


Fig. 7. BLOOD PIGMENTS in patient *M. S.*

(including hemoglobin) between 4.6 and 5.6 gm. per cent during the whole course of the hemoglobinemia. The hematocrit value observed in the control sample was 17. As hemoglobin-saline was infused the hematocrit progressively fell, until values as low as 5.5 were obtained. For 30 hours the values were between 5.5 and 7. This patient lived because of

the hemoglobin dissolved in the plasma, which supplemented the oxygen capacity of the intracorporeal hemoglobin.

The reticulocyte count increased rapidly in this patient, reaching a peak of 12 per cent after 30 hours. The values are shown in figure 7. Plasma methemoglobin was also determined and is shown in figure 7. Its concentration rose only slightly during the whole course of the hemoglobinemia.

Kidney block became evident very early. Urine volume declined to less than 5 cc/hr. and remained at this low level for four days. The block failed to respond to all treatment, including whole blood transfusions. Nerve block on the 5th day was followed by an increase in urine volume to 10 cc/hr. Clinical signs of uremia appeared on the 6th day. The patient died at 9:10 A.M. on the 9th day after delivery, showing a terminal 2:1 heart block. Terminal NPN was 220; BUN was 190.

Renal failure in such a case is to be expected, even when no hemoglobin has been given. Young (27) has described similar obstetrical patients, and Adam (28) has reviewed the literature. In this case there were no less than five factors, recognized in the literature as able to cause oliguria: pre-eclampsia, retro-placental hemorrhage, retained placenta, massive post-partem hemorrhage with shock, and putrid endometritis of mild form.

This case has done more than any other in our series to demonstrate both the possibilities and limitations of intravenous injections of hemoglobin-saline. It justified our expectation that our solution might be effective clinically in raising blood pressure and restoring blood volume after extensive hemorrhage, confirming our earlier animal experience (2). It showed that hemoglobin in solution in the plasma is able to transport oxygen, in man as in animals. It established a new high level for volume of fluid and weight of hemoglobin injected.

*Kidney Damage after Hemoglobin-saline Injections.* In our series of 14 cases we have injected hemoglobin-saline 77 times. Seven cases—those most fully and carefully studied—have received multiple injections, numbering 3, 5, 9, 10, 12, 13 and 18 times, respectively, and totaling 70 times. In only one of these cases did oliguria occur, namely in the case of shock (5 injections) where the circumstances were sufficiently complicated to make a judgment as to the causative factor impossible. In seven other cases only single injections were made. Oliguria was observed in one of these, as the result of the injection of a toxic solution, the patient later recovering. These figures suggest that impairment of urine flow by hemoglobin-saline is exceptional, contrary to the fears of some critics.

In addition to the kidney damage observed in the case of shock, 3 of the 6 other multiply injected patients have shown transient rises in NPN and decreased urea clearances, without oliguria. Indications of this character emphasized again the desirability of securing more extensive and detailed information concerning kidney function, by methods more precise than those routinely used in clinical laboratories. We attempted therefore to determine glomerular fil-



tration rate, renal plasma flow and tubular Tm values, using the clearances of mannitol and paramino-hippuric acid (PAH) according to the procedures of Homer Smith and his colleagues (25, 26). By these methods we have studied 2 patients, one in only a preliminary fashion, the other more thoroughly.

TABLE 1. RENAL CLEARANCES IN CASE 11

DATE	FILTRATION RATE	BLOOD FLOW	FILTRATION FRACTION	Tm
	<i>cc/min.</i>	<i>cc/min.</i>	<i>%</i>	<i>mg. PAH/min.</i>
9/27/43	85.9	530.9	16.2	70.4
	87.7	492.3	17.9	72.0
10/ 4/43	84.6	542.6	15.6	59.5
	85.1	504.2	16.9	67.7
10/25/43	73.1	419.6	17.4	56.0
	72.2	439.9	16.4	57.9
11/ 7/43	<i>200 cc. sterile hemoglobin-saline solution</i>			
11/ 8/43	26.9	174.4	15.4	21.3
	22.8	173.0	13.2	18.7
11/11/43	31.3	167.7	18.7	20.2
	30.7	173.3	17.7	20.4
11/15/43	34.0	208.6	16.3	18.0
	32.0	169.1	18.9	16.4
11/22/43	47.3	252.1	18.8	32.8
	48.2	254.3	19.0	29.7
11/30/43	57.8	290.8	19.9	32.2
	56.0	265.6	21.8	31.1
12/13/43	67.0	319.9	20.9	38.6
	67.5	339.4	19.9	38.1
12/28/43	72.9	373.0	19.5	49.9
	69.9	327.6	21.3	47.5
1/11/44	75.1	486.1	15.4	58.6
	82.4	477.7	17.3	60.1

In the first case we secured only a reading on renal plasma flow by PAH. The pressor rise and bradycardia in this case, S. L., after infusion of 150 cc. of hemoglobin-saline, are shown in figure 1. Four readings on renal plasma flow before infusion gave 1054, 993, 1208 and 955 cc. On the day after infusion values of 1222 and 1030 cc. were secured. There was no evidence of any impairment in this function.

The second case, *E. P.*, was that of a 60-year-old white female, long a patient in the Baltimore City Hospitals, suffering from rheumatoid arthritis and hypertension. After preliminary studies of renal function a single injection of 200 cc. hemoglobin-saline (24 gm. hemoglobin) was made. Cardiovascular data immediately after injection are shown in figure 1. Twelve determinations of mannitol and PAH clearances were made, three before and nine after infusion. The data are shown in table 1.

It will be seen that the infusion of our solution led to very appreciable diminutions in glomerular filtration rate, renal plasma flow and  $T_m$ , to about one third of the original levels. The effect persisted for many days, recovery to original levels occurring only after two months. Urine volume was well maintained throughout, rising somewhat in the first day, and continuing thereafter within normal limits.

Our experience with this last case forced us to recognize that the more precise modern renal methods may disclose impaired function which the routine tests, such as the NPN, the BUN and the urea clearance, either fail to detect or indicate very inadequately. In many laboratories the routine clinical tests are considered sufficient to determine significant renal damage. After this experience we have not been content so to consider them. We feel that more clinical cases must be studied, with careful attention to renal function by the modern methods. We believe that an acceptable hemoglobin-saline solution must not cause such change in glomerular filtration rate, renal plasma flow and  $T_m$  values as we observed in this last case.

In three cases liver function was tested by Quick's hippuric acid method (23). Values were within normal limits before and after hemoglobin-saline injection.

*Hemoglobin Derivatives before and after Injection.* Critics of the use of hemoglobin-saline solutions have feared the presence in them of toxic breakdown products, derived from the pigment molecule. We have not made a thorough search for such toxic substances, nor have we been led to accept the thesis that some such factor is sure to be present. However, the possibility of the occasional appearance of such toxins must be recognized.

Porphyry at once occurs to mind as a possible toxic material. Dr. Frank H. J. Figge, of our Department of Anatomy, determined the concentration and type of porphyry present in two of our solutions and found them to contain 66  $\gamma$  and 124  $\gamma$  per 100 cc.—amounts not greater than those normally present in blood. Spectroscopic examination disclosed only the relatively non-toxic protoporphyrin.

Methemoglobin is also routinely present in our solutions to the extent of 2 per cent of the total pigment. Similar percentages are found in normal blood. Some years ago we described (2) a slow increase of methemoglobin in the plasma of cats after the intravenous injection of hemoglobin-saline. At death it often

constituted half of the pigment remaining in the plasma. These older experiments were made with solutions containing hemoglobin derived from beef cells. We had feared a similar rise in the concentration of methemoglobin in our clinical cases. Fortunately human hemoglobin does not behave like beef hemoglobin. We have been able to study its behavior in two of our human cases, in which hemoglobinemia endured for many hours. The data obtained in patients *H. C.* and *M. S.* are shown in figures 3 and 7. We have made similar observations in many animal experiments when human hemoglobin was injected. Very little change occurs in the absolute concentration of methemoglobin, which remains low throughout. In all multiply-treated cases in our clinical series and in all similar animal experiments, there has never been any evidence of anaphylactic reaction to the infused hemoglobin-saline solution.

#### DISCUSSION

In spite of the hazards undoubtedly present in the preparation and clinical use of hemoglobin-saline solutions, our data suggest the following favorable indications: 1) Such solutions have been given repeatedly to the same human subject, by intravenous injection, in volumes and weights of hemoglobin far exceeding any previously reported in the literature, without evidence of anaphylaxis. 2) These solutions do not agglutinate cells of the four main blood groups. 3) Injected into uncomplicated cases of secondary anemia, they stimulate hematopoiesis. 4) They exert a colloidal osmotic pressure which enables them to restore lost blood volume and raise blood pressure. 5) Dissolved hemoglobin transports oxygen much as it does when confined within the red cell and so augments the oxygen capacity of the blood. 6) Methemoglobin does not accumulate in the plasma even after large injections of these solutions.

The best hope for the therapeutic use of hemoglobin-saline solutions may lie in the direction of the stimulation of hematopoiesis by multiple infusions of small volumes over many days. Such stimulation has repeatedly been reported in animal experimentation (29). It was to be expected in man, but has not previously received clinical demonstration. In our series five cases of secondary anemia due to hemorrhage or infections were treated. In three of these definite improvement was seen. The other two cases had concomitant hemorrhage at the time of infusions so that the beneficial effect of hemoglobin-saline, if present, could not be evaluated. In two other cases of anemia, one with lymphatic leukemia and the other with agnogenic myeloid metaplasia, no improvement was observed from repeated injections.

The value of these solutions in the treatment of shock is more uncertain. Our experience with shock is limited to a single case and is obviously insufficient to establish the solutions as a therapeutic aid for this condition in man. The observations on this case can be considered as suggestive only, although they appear to establish several fundamental points, particularly 4, 5 and 6 above.

We consider that solutions containing 10 to 12 per cent of hemoglobin are best for such work, although their colloidal osmotic pressure is somewhat higher than that of normal plasma.

The only experimental study of the efficacy of hemoglobin-saline solutions in the treatment of shock in animals is the recent report of Lamson *et al.* (30). These workers were able to save dogs after very severe hemorrhage if the solutions were given quickly. Their results confirm our own animal experience in demonstrating that very large substitutions of whole blood by hemoglobin-saline are possible (in our series up to 90 %) without causing shock or renal impairment. These favorable results call into question such adverse findings as those of Flink (31), who injected large quantities of hemoglobin solutions into normal dogs without removing blood and followed renal changes by serial biopsies. By his technique he induced extreme hyperemia, sufficient in itself to cause damage to many tissues.

In spite of favorable indications in some of our human cases, we are forced to recognize that we have not yet succeeded in producing benign solutions routinely. We have made solutions which passed all animal tests but which nevertheless gave reactions when used clinically. At the present time we do not possess an animal test which will surely protect the human subjects. The reasons for these difficulties remain in doubt, but the following possibilities may be recognized:

- 1) Bacterial contamination of hemoglobin-saline solutions is an ever present hazard. The original red cells are not always absolutely sterile. Every step in the process of preparation must be carefully guarded, since the solutions furnish a very favorable culture medium for many organisms.

- 2) Even in sterile solutions, or later, after injection into the blood stream, the hemoglobin molecule may be modified or transformed and may then give rise to toxic derivatives. We know very little about the conditions which permit such products to form, but their appearance in the circulating blood, and their connection with definite pathology, has certainly been established in some cases reported in the literature.

- 3) Constituents of the red cell other than the hemoglobin may pass into the solutions and exercise a deleterious influence. Among these are the remnants of the stroma proteins. The enzymes of the red cells must also in part enter our solutions and may there become modified or denatured.

A considerable literature deals with such hemoglobin derivatives as those mentioned in possibility 2. In a long series of papers Barkan and his collaborators (32, 33) claimed the existence of a type of hemoglobin from which the iron may be more readily removed than from ordinary oxyhemoglobin. The hemoglobin moiety containing the 'leicht abspaltbare Bluteisen', or labile iron, is no more than 5 per cent of the total pigment. This modified hemoglobin molecule, known as 'pseudo-hemoglobin', seems to be a first step toward the

formation of bilirubin. The existence of such a modified hemoglobin, even within the normal red cell, has been confirmed by Lemberg and his colleagues (34), who have secured spectrophotometric evidence for the presence of a 'bile-pigment hemoglobin' which they name 'choleglobin'. In this derivative the porphyrin ring of the prosthetic group has broken by oxidative scission, but remains attached to its globin. Later, within cells of the reticulo-endothelial system, the modified prosthetic group of choleglobin breaks from its protein, loses its iron and is transformed through biliverdin to bilirubin. This sequence of chemical change appears to be the normal and preferred route for hemoglobin degradation. No evidence is given in this literature that choleglobin or any of its breakdown products are toxic. Certainly bilirubin is not. According to Bomford (35) intravenous injections of bilirubin stimulate hematopoiesis in anemic dogs. Weech, Vann and Grillo (36) have injected considerable amounts of bilirubin into human cases with no indications of toxicity.

Hemoglobin may, however, break down along a second chemical pathway. Methemoglobin, containing iron in the ferric form, is normally present in small amounts within the red cells (37). From its molecules hematin (ferrihemate) may split off. Hematin, losing its iron, may become protoporphyrin. Various agents, such as the sulfonamides which produce methemoglobinemia, may also increase the blood concentration of these derivatives without the appearance of bilirubin (38).

In our studies of the nearly complete replacement of blood in cats by beef hemoglobin-saline, death was definitely anoxic in character and was related to the terminal concentration of dissolved hemoglobin in the blood stream (about 3 gm. %), not to the amount of methemoglobin then present. The terminal values for methemoglobin varied considerably. In the longer survivals methemoglobin sometimes rose to a value of 3 gm. per cent. In our clinical studies human methemoglobin dissolved in the plasma has never risen to such heights. The concentration remained nearly constant at the low level originally present (0.2-0.3 gm. %). A similar behavior of human methemoglobin has been observed after injection into animals. It is therefore very unlikely that the reactions so observed in some of our cases are due to methemoglobin.

Such evidence as we can discover in the literature suggests that methemoglobin is not an actively toxic agent. Its physiological effects arise from the oxygen deficit associated with its presence (39). Not only is the oxygen capacity of the blood reduced, but the oxygen dissociation curve of hemoglobin is shifted to the left (40), both in solution and within the red cells, so that oxygen unloading in the tissues is retarded. Bing (41) shows that methemoglobin does not create a kidney block in dogs except when an experimental acidosis has been induced by oral administration of ammonium chloride, to give a urine more acid than pH 5.8.

When methemoglobin breaks down to form globin and hematin, a number

of new possibilities confront us. Schumm (42) found hematin regularly present in the blood of pernicious anemia patients and it has even been considered a diagnostic test for this disease. Hematin is formed within the cells of the malarial parasite (43) and thence liberated into the blood stream. Duesberg (9), using rather small injections of hemoglobin, was unable to detect hematin formation in normal men, although bilirubin increases were easily seen. He argued that the two substances cannot be on the same pathway of breakdown of the hemoglobin molecule; i.e. that bilirubin cannot arise from hematin. In all cases of liver disease involving destruction of the parenchyma, however, Duesberg detected hematin formation after hemoglobin injections. Fairley (44) claims that in primate blood the Schumm test demonstrates the presence, not of free hematin but of a new pigment, methemalbumin (first detected in cases of backwater fever), which forms when hematin joins with plasma albumin. It does not appear in the urine. The existence of such a pigment, differing from hematin, has been fully confirmed by the spectroscopic studies of Foy and Kondi (45) and others.

In animals hematin may be very toxic. Anderson *et al.* (46) report that hematin produces acute and chronic changes in the kidneys and in the reticulo-endothelial and vascular systems. The observed lesions can be accounted for by multiple small thrombi, without invoking any intrinsic toxicity of ferrihemate. These authors cannot detect any combination of hematin with plasma proteins, in agreement with Fairley, who found such a union only in primates. Nevertheless, hematin does not appear in the urine, but is deposited in cells of the reticulo-endothelial system.

The rôle of the liver must be kept in mind in all discussions of the fate of intravenously injected hemoglobin-saline solutions. Scheff (47) has found that the formation of methemoglobin *in vivo* by aniline is diminished by hepatectomy. The rapid increase of ferritin iron in these organs in dogs, after partial hemolysis of red cells by phenylhydrazine, has been observed by Hahn *et al.* (48).

It seems fair to conclude, from this literature, that when, and if, hematin appears in the human blood stream it will be quickly engulfed by cells of the reticulo-endothelial system, particularly in the liver, bound as methemalbumin and so rendered innocuous. In the absence of disease of the liver, or when it is overwhelmed by massive hemoglobin injections, free hematin may appear in the plasma and produce lesions. Hematin, losing its iron, becomes porphyrin, some types of which are toxic. Our solutions contain only traces of relatively non-toxic protoporphyrin. The observations of Kark and Meiklejohn (14) suggest that hemoglobin does not readily degrade to porphyrin within the blood stream; the porphyrinuria of plumbism does not arise from hemoglobin breakdown.

An important condition controlling the breakdown of the hemoglobin

molecule is the acid-base equilibrium in blood and urine. Baker and Dodds (49) on the basis of experimentation with rabbits concluded that hemoglobin and its derivatives, particularly methemoglobin and hematin, mechanically block the renal tubules when precipitated from an acid urine. They advocated the administration of alkali to prevent such a result. De Gowin and his associates (50), using dogs, reported that they could substantially confirm Baker and Dodds, but recognized that mechanical obstruction of renal tubules was not sufficient to explain all of their deaths. They inferred the presence of a nephrotoxic factor, able to cause necrosis of tubular epithelium. They have, however, been opposed by Bing (41) and by De Navasquez (51), who could not confirm Baker and Dodds in animal experiments.

The ideas of Baker and Dodds have been accepted by many clinicians, most recently by Bywaters (52), who urges administration of alkali in treatment of the crush syndrome, and by Shen, Ham and Fleming (53) in management of burn cases. They have been opposed by other clinicians (45, 51, 54). Our own patients have generally received alkali. We have given a number of injections without alkali and have seen no difference in the results. In some of our cases the urine turns alkaline even without alkali administration. Bing (41) observed similar alkaline urines in his acidotic dogs, after induction of oliguria. The phenomenon may be a sign of renal pathology. The proper procedure in management of the cases remains in doubt. Such an alkaline shift in the urine is certainly not typical of all clinical conditions accompanied by hemoglobinemia. Ross (55), for instance, in his classical study of black-water fever, could detect no acidosis in the blood, but found the urine to be acid in every case.

It must be emphasized that almost every investigator in this field has used a different method for the preparation of his hemoglobin-saline solutions. Conflicting results and claims have therefore inevitably arisen. A standard hemoglobin solution is needed, prepared in such a way that its stability is insured. The field is a difficult one, beset with many hazards. More clinical studies are needed. This record and argument are set down for the benefit of those who may attempt them, as guidance and warning.

#### SUMMARY

A method is described for the preparation of hemoglobin-saline solutions for intravenous injections in clinical cases. The results of such injections into 14 patients are described. Seven patients received more than one injection, 7 other patients only one.

In the multiply injected group there were 5 cases of secondary anemia due to hemorrhage or infection. Of these, 3 patients showed definite improvement after treatment, exhibiting reticulocytosis and an increase in blood hemoglobin and hematocrit values (fig. 5). In a 4th patient the effect of the injections could not be evaluated, since hemorrhage continued. In none of these four

cases did oliguria develop. In a 5th patient (figs. 6 and 7) the secondary anemia developed from a severe hemorrhage post partum, which led to a state of shock. Administration of hemoglobin-saline (2300 cc. in 5 injections) restored blood pressure to normal. The patient appeared to be recovering, but developed oliguria and uremia and died on the 9th day.

In one case of lymphatic leukemia and one of agnogenic myeloid metaplasia no improvement was observed after repeated injections. Urine flows remained normal. In the singly injected group no beneficial effects were observed. One patient showed oliguria, with recovery.

Although definite oliguria was observed in only two cases out of the 14 treated, indications of renal impairment (by NPN or clearance values) were observed in three other cases of the multiply injected group and one of the singly injected group. In the latter case, after injection of 200 cc. of hemoglobin-saline, glomerular filtration rate, renal plasma flow and  $T_m$  were reduced to about one third of the original values, with later recovery to normal. Liver function remained normal in the three cases tested. In some cases injections up to a volume of 500 cc. (= 50 to 60 gm. hemoglobin) have given no rise in temperature or other reactions. In other cases pyrogenic reactions have been observed, usually mild, but occasionally severe, complicated by other reactions. The effect of single injections upon temperature, for 7 patients, are shown in figure 1. In 6 patients the average amount of hemoglobin which appeared in the urine (27 tests) was 18 per cent of that injected (fig. 4).

The following favorable indications have also been observed: 1) Such solutions have been given repeatedly to the same human subject, by intravenous injection, in volumes and weights of hemoglobin far exceeding any previously reported in the literature, without evidence of anaphylaxis. 2) These solutions do not agglutinate cells of the four main blood groups. 3) They exert a colloidal osmotic pressure which enables them to restore lost blood volume and raise blood pressure. A chemical pressor principle is also present. The pressor effect endures for several hours. The rise in blood pressure is accompanied by decrease in heart rate (figs. 1 and 2). 4) Dissolved hemoglobin transports oxygen much as it does when confined within the red cell and so augments the oxygen capacity of the blood. 5) Methemoglobin does not accumulate in the plasma even after large injections of these solutions (figs. 3 and 7).

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## *Interval of Useful Consciousness at Various Altitudes<sup>1</sup>*

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USEFUL CONSCIOUSNESS means that state in which the individual remains attentive and is able to perform useful or purposeful acts. While this is an arbitrary definition it appears that a fairly definite end point exists between the state of useful consciousness and the state which extends to complete loss of consciousness. In fact, it seems that the end point of useful consciousness can be determined with greater definiteness than that for total loss of consciousness. MacKenzie *et al.* (1) have reported noteworthy experiments and have discussed the significance of useful consciousness in anoxia. Ruff and Strughold (2) discuss many experiments of this nature. Accurate appraisal of the factors which influence useful consciousness states in flyers under stress of anoxia is of fundamental importance in aviation.

There are three distinctly different ways to study the effect of altitude on the interval of useful consciousness: 1) by changing the ambient pressure while the subject continues to breathe pure oxygen at the ambient pressure; 2) by changing the ambient pressure while the subject continues to breathe ambient air; and 3) by maintaining a constant ambient pressure while the subject changes from breathing pure oxygen to breathing ambient air.

The latter type was used in this investigation and two different studies are reported. The first is a record of determinations of the interval of useful consciousness at various altitudes as a criterion of altitude tolerance. The second represents an attempt to induce an increase in tolerance to altitude by raising the oxygen capacity of the blood by transfusion. Pace *et al.* (3) have shown that an artificially induced polycythemia increased tolerance to hypoxia when estimated on the basis of the pulse rate during exercise under conditions of lowered oxygen tensions.

### METHODS

It was considered that a method should be devised that would measure the interval of useful consciousness as accurately and be as simple of interpretation as possible. In the method used, the subject had no difficulty in making

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<sup>1</sup> Work done under contract with the Physiology Branch, Aero-Medical Laboratory, Materiel Command, Wright Field.

a perfect score while in a state of useful consciousness. When he failed, he failed almost completely to score accurately even though he had not completely lost consciousness. Thus the scoring was simple. Since the responses were only one and one-third second apart, end points were determined to within narrow limits. Permanent records were also obtained.

*Useful Consciousness Time Recorder.* The apparatus used in these studies consisted of the following components: a selector switch, a projection box, response keys and a recording camera. The selector switch was used to close the circuit of each of four projectors at random, but to leave the circuit closed for one second with an interval of one-third second between flashes. The four lights were used to project on a six-inch screen placed before the subject, images of the four symbols respectively. Each of the four response keys were similarly marked with the symbols. A camera recorded photographically the image flashed and the subject's response. The camera also recorded other events such as breathing patterns and, consequently, all important information was properly recorded as to time and became a permanent record of events. The selector switch and camera were placed outside of the low pressure chamber, while the projectors and response keys were within. A more detailed description of this apparatus will be published elsewhere.

These studies were carried out in a low-pressure chamber with the subject and observer sitting on a bench before the projection screen. Simulated altitudes were obtained with two calibrated and properly corrected altimeters. A Pauling oxygen meter was used to check the altitude and to ascertain the correct partial pressure of oxygen in the air to be inspired by the subject. An arrangement was made which permitted the observer to divert the oxygen supply to ambient air instantaneously. Analyses of gases within the mask showed that, after the first complete breathing cycle following interruption of the oxygen supply, only air of normal atmospheric composition was being breathed. Following loss of consciousness the oxygen supply was restored with a small free flow of oxygen made available to the subject's mask. Thus resuscitation was accomplished quickly. This was an important factor in giving confidence to the subject and reducing apprehension to a minimum. Pulmonary ventilation records indicate very little apprehension during the course of the tests.

Subjects were instructed to operate response keys for two minutes before interruption of the oxygen supply. They did not know when the oxygen supply was interrupted. They continued to respond to signals until loss of consciousness. Most of the subjects disclaimed knowledge of loss of consciousness. All subjects could make perfect scores at all altitudes up to and including 42,000 feet while breathing oxygen. The end point of responses was sharp and rarely did a subject make two successive failures without complete failure, and loss of consciousness ensued within a few seconds thereafter.

## EXPERIMENTAL SUBJECTS

*Study I.* Ten healthy men ages 20 to 26 years were selected as subjects. Each was given training and experience in exposure to simulated high altitude in a low-pressure chamber. Subjects were taken to altitude individually and records made at each of the altitudes under investigation. No subject was given more than one exposure to low oxygen pressure

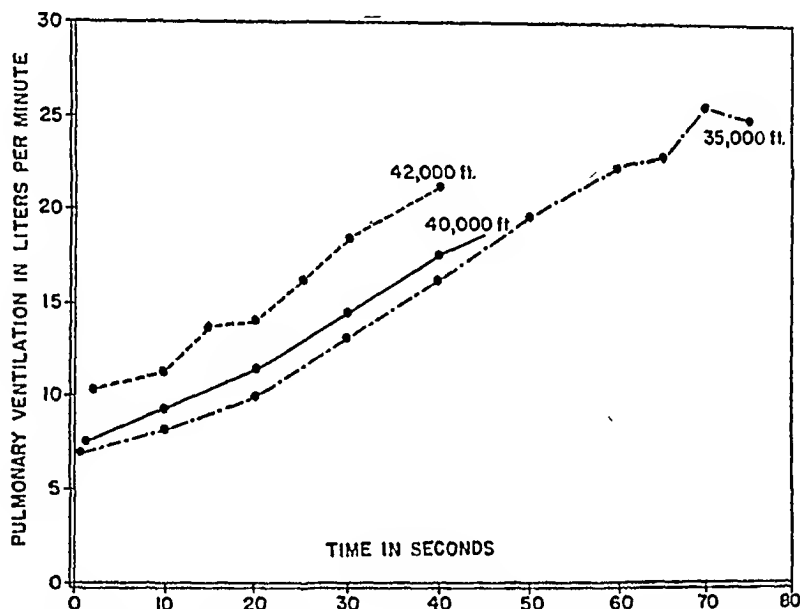


Fig. 1. PULMONARY VENTILATION of subject breathing air at three different altitudes

TABLE I. HEMOGLOBIN CONCENTRATION IN BLOOD OF EXPERIMENTAL SUBJECTS BEFORE AND AFTER TRANSFUSIONS

SUBJECTS	GRAMS HB/100 ML. BLOOD	
	Before transfusion	After transfusion
<b>DONORS</b>		
H. M. D.....	14.6	13.5
F. F.....	15.2	13.5
J. P. G.....	16.0	13.4
D. C. M.....	15.5	13.0
<b>RECIPIENTS</b>		
A. L. B.....	15.6	16.5
J. G.....	15.5	17.1
R. L. L.....	15.0	16.7
B. M. M.....	16.0	17.0
J. W. W.....	16.0	17.4

per day and all were in good nutritional states. None showed any untoward effect of the experiment. Three exposures to each altitude was adopted as the routine procedure.

*Study II.* Nine healthy men ages 20 to 25 were selected for subjects for blood studies after complete examination by the Hematology Department of the Duke Hospital. Four of these subjects volunteered as blood donors and 5 as blood recipients for the transfusion experiments. One liter of blood was withdrawn from donors and 500 ml. of 'packed' cells

were transfused into recipients. This was accomplished in two stages with a 24-hour interval between transfusions. The time of useful consciousness was determined for each subject breathing air at 35,000 feet as previously described.

Blood analyses consisted of hemoglobin determinations by spectrophotometer, oxygen capacity by the Van Slyke manometric procedure, R.B.C. counts and hematocrit determinations. Several analyses were made before and after transfusions. Oxygen capacity values agreed very closely with the hemoglobin determinations. Consequently, for simplicity only the hemoglobin values are presented (table 1).

Both donors and recipients were taken to altitude on the second day following transfusion and a series of five exposures were made within seven days following transfusion. Not more than one test was made per day. All subjects completed the series without mishap. One donor and one recipient reported moderate headaches on two successive days.

*Pulmonary Ventilation during Interval of Useful Consciousness.* It is known that certain levels of hypoxia lead to increases in the pulmonary ventilation with concomitant effects upon altitude tolerance. Consequently it was thought desirable to have determinations of pulmonary ventilation in these experiments. The subjects wore the standard Air Force A-13 oxygen mask throughout each experiment. This made it possible to switch from pure oxygen to ambient air, to record breathing patterns continuously and to accomplish rapid resuscitation following loss of consciousness. From the breathing patterns recorded it was possible to calculate and construct integrated curve of pulmonary ventilation for each five-second interval during the hypoxic state of the subject. This method will be described in a later report. Figure 1 illustrates the changes in pulmonary ventilation during the interval of useful consciousness following loss of the oxygen supply while the subject is breathing air at the ambient altitude.

## RESULTS AND DISCUSSION

The results of Study I are shown in figure 2. Statistical analyses were made to determine the standard deviation shown in figure 2. It will be observed that at a 35,000-foot altitude and above the duration of useful consciousness bears almost a linear relationship to the barometric pressure. This indicates that the quantity of reserve oxygen in the lungs is the principal limiting factor. Figure 1 shows that the 'anoxia drive' in respiratory regulation begins quickly and proceeds with greater intensity during the anoxic state at least until consciousness is lost.

The results of Study II indicate that an induced state of acclimatization can be produced by means of blood transfusion. The results are summarized in table 2. It will be noted that loss of blood oxygen capacity decreases the interval of useful consciousness and gain of blood oxygen capacity increases the interval of useful consciousness. This occurred in all subjects without exception. Increases and decreases in tolerance to altitude in individuals reported cannot be attributed to variations in pulmonary ventilation as is evident in figure 3, since changes in ventilation before and after transfusions are not significant.

Because tests were made only at a single altitude one cannot say with assurance just what degree of tolerance was accomplished by blood transfusions.

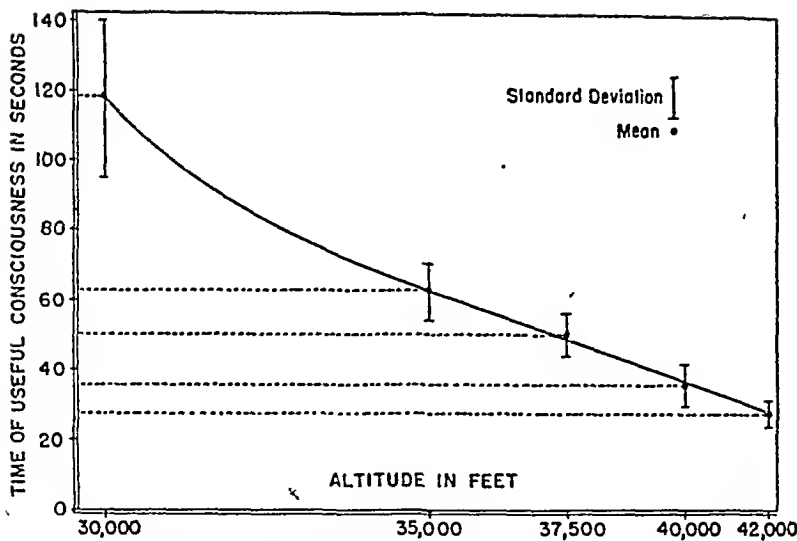


Fig. 2. Time of useful consciousness at various altitudes

TABLE 2. TIME OF USEFUL CONSCIOUSNESS WHILE BREATHING AMBIENT AIR AT ALTITUDE. SUBJECTS BEFORE AND AFTER BLOOD TRANSFUSIONS

SUBJECTS	SECONDS OF USEFUL CONSCIOUSNESS	
	Before transfusion	After transfusion
DONORS		
H. M. D.....	55	47
F. F.....	62	55
J. P. G.....	62	58
D. C. M. <sup>1</sup> .....	50	45
RECIPIENTS		
A. L. B. <sup>1</sup> .....	38	45
J. G.....	65	77
R. L. L.....	69	81
B. M. M.....	59	71
J. W. W.....	67	73

<sup>1</sup> These subjects were tested at 37,500 feet altitude. All others at 35,000 feet altitude.

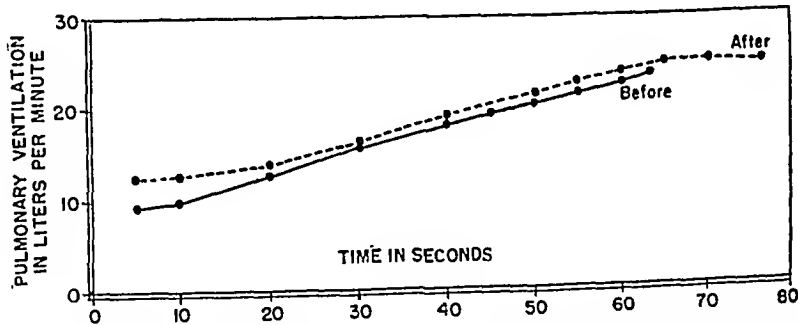


Fig. 3. PULMONARY VENTILATION in subject breathing air at 35,000 ft. altitude, before and after blood transfusion

If one projects the values obtained in Study II to the figure 2 obtained in Study I, it would appear that an approximate gain in tolerance of 2000 feet occurred in recipients and loss of 2000 feet occurred in donors.

Criteria used for determination of the end points of useful consciousness have not been adequately studied. Consequently, it is difficult to compare results obtained by different authors. The results presented here are in general agreement with those of MacKenzie *et al.* (1) and Webster and Reynolds (4). When writing tests are used slightly shorter intervals of useful consciousness are obtained. Writing tests in which numbers are written involve retention and different levels of conscious activity than those involved in simple mechanical responses to external visual stimuli. It is believed that the method employed in these studies offers certain advantages in that consistent and accurate recorded results can be obtained on subjects with a minimum of training. Further study is required, however, to properly evaluate criteria used by different investigators.

Two practical aspects of this problem appear to the writer. First, 'artificial' or 'induced' acclimatization to altitude is a possible means of increasing tolerance to altitude. Second, that wounded individuals who have lost blood will have a decreased tolerance to anoxia.

#### SUMMARY

The interval of useful consciousness following interruption of oxygen supply is used as the criterion for altitude tolerance. A means for measuring this time is described. The interval of useful consciousness of each of 10 healthy young men was determined at the following altitudes while breathing air: 30,000, 35,000, 37,000, 40,000 and 42,000 feet. The oxygen capacities of the blood of 4 healthy young men were lowered from an average of 15.3 gm. to 13.3 gm. of hemoglobin per 100 ml. of blood by blood-letting. In a similar group of 5 men oxygen capacities were increased from 15.6 to 17.0 gm. of hemoglobin per 100 ml. of blood by blood transfusion. The interval of useful consciousness while breathing air at 35,000 feet altitude was determined for each individual of the above groups, before and after transfusions. It is concluded that induced changes in the oxygen capacity of the blood modify tolerance to altitude when useful consciousness is used as the index.

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# *Effects of Physical Hyperthermia Upon Blood Gas Equilibria in Man<sup>1</sup>*

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THE INFLUENCE OF ELEVATED BODY TEMPERATURE on oxygen and carbon-dioxide equilibria in the blood may be considered most simply as the sum of the modifications in physico-chemical equilibrium caused by change in temperature plus the physiological variations brought about by adjustments in the central nervous system, the circulation and salt and water exchange. A precise understanding of the overall changes and the various factors entering into them is of importance in the fields of exercise and climatic physiology as well as in medicine, i.e. in clinical and therapeutic fever.

The fever studied in this work was induced by external heat at rest ('physical hyperthermia'). The conclusions should apply to febrile conditions caused by other means where, however, under these circumstances, factors in addition to fever play a larger part in the overall picture.

The effect of temperature changes on the physico-chemical equilibria of blood was summarized by Dill and Forbes (1) for temperatures below normal; logical extrapolations can be made to higher temperatures. Actual measurements above 37 to 38°C. have been less complete. The established qualitative changes are *a*) decreased affinity of hemoglobin for oxygen with rise in temperature, originally reported by Brown and Hill (2) and *b*) a combination of decreased solubility of CO<sub>2</sub> and decreased alkali reserve, thus with little change in *pH* (1).

The majority of physiologic reports (3) agree that both in experimental animals and in man, increased pulmonary ventilation occurring during fever results in a decrease in CO<sub>2</sub> content and a rise in *pH* of the arterial blood. The degree of alkalosis reported has a wide range. This variability, as well as that in the reported alkali reserve, probably is due to *a*) differences in duration of fever, with accumulation of fixed metabolic acids after longer durations (4-7), *b*) to the use of variable amounts of sedative drugs, which variable has been mentioned only once in the reports on fever in man (7), and *c*) to possible technical inadequacies particularly in electrometric *pH* measurements.

Even in the presence of hyperventilation alkalosis it has been contended that there is an arterial anoxia in uncomplicated fever. Reports on animals to this effect may be ex-

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plained by the moribund condition of the animals with secondary changes in the lungs (8) or by the extremely shallow tachypnea not seen in man (9). The evidence for arterial anoxia in humans rests largely on the work of Cullen *et al.* (10). They found no significant unsaturation of the arterial blood, but concluded from calculations that the  $pO_2$  was lowered by 30 per cent. Their calculations, however, have several weak points: 1) failure to take into account the lowered affinity of hemoglobin for oxygen at higher temperatures; 2) utilization of the standard oxygen dissociation curve at their observed  $pCO_2$  at  $38^\circ C.$ , disregarding changes in solubility of  $CO_2$  and in alkali reserve due to altered temperature; 3) the unreliability of the standard oxygen dissociation curve in the upper portion in predicting the equilibrium in any single blood.

Although a complete study of  $CO_2$  and oxygen exchange should include estimations of the mixed venous blood and probably venous blood from various vital organs, the detailed study of arterial blood to be reported here will afford clarification of most of the physico-chemical factors and an important segment of the physiological factors, i.e. those relating to pulmonary function.

#### METHOD

Fever was induced in the Emerson hot, humid-air cabinet. The time to attain a body temperature of  $40^\circ C.$  was 80 to 120 minutes. After an additional period of 30 to 90 minutes a sample of arterial blood was withdrawn. Usually the temperature at this time was  $40.6^\circ C.$ , but in a small number of cases varied from  $40.1$  to  $41.2^\circ C.$

For control studies, blood was withdrawn at the bedside on a different day from that in which fever studies were carried out. It is realized that it would have been ideal to take control bloods immediately before the induction of fever. Although limitations of time for analysis dictated our procedure, it is true that, of the measurements made, only the alkali reserve might be expected to show significant day to day variations, due to inconstant daily diet. On the other hand, in our patients, arterial gas tensions, which were our main concern, are dependent chiefly on pulmonary function and, therefore, would be expected to remain constant from day to day.

Eight male subjects ranging in age from 25 to 55 years were studied. Two were normal. Five received physically induced fever for neurosyphilis and one, for a non-specific iritis. No cardiovascular or pulmonary diseases could be detected by the usual clinical tests.

A total of 15 arterial blood samples were analyzed and studied at elevated body temperatures on these 8 subjects. Control bloods at normal body temperature were obtained on 6 of the 8.

While subjected to physical hyperthermia patients are usually given sedation to allay the restlessness and discomfort entailed in this procedure. Early in the course of our investigations, it was noted that sedated patients exhibited somewhat higher carbon-dioxide tensions than ineffectually sedated patients. For this reason six of the experiments during fever on as many subjects were

tension of  $\text{CO}_2 = 43.2$  mm. Hg at  $40.5^\circ\text{C}$ . yields the required value of 2.78 volumes per cent. This is designated as  $T_{43.2}$  for comparison with  $T_{40}$  at  $37^\circ\text{C}$ ., and affords a concentration of acid equal to the latter (table I). When respective  $\text{CO}_2$  capacities are now compared it is obvious that the combining power of the blood is about 1.3 volumes per cent less, rather than 2.9 (table I).

These considerations can equally well be extended to embrace the entire  $\text{CO}_2$  absorption curve. This is graphically illustrated in figure 1a, b, which summarizes the average values of two experiments on normal blood equilibrated at  $37^\circ$  and  $40.5^\circ\text{C}$ . Thus, when equal  $\text{CO}_2$  tensions are plotted logarithmically against serum bicarbonate at the two temperatures in question,

TABLE I. ANALYSIS OF THE EFFECT OF ELEVATION OF TEMPERATURE ON THE ACID-BASE PROPERTIES OF BLOOD

SUBJECT	BODY TEMP.	I $T_{40}$ AT $37^\circ$	II $T_{40}$ AT $40.5^\circ$	III $T_{43.2}$ AT $40.5^\circ$	$\Delta$ II-I	$\Delta$ III-I
	$^\circ\text{C}$ .	vol. %	vol. %	vol. %	vol. %	vol. %
C. K.....	37	51.1	48.8	50.4	-2.3	-0.7
C. K.....	40.1	47.2	45.5	47.1	-1.7	-0.1
J. G.....	37	49.1	46.1	47.7	-3.0	-1.4
J. G.....	40.2	47.2	44.1	45.7	-3.1	-1.5
E. G.....	37	48.7	45.3	46.9	-3.4	-1.8
E. G.....	37	46.9	43.4	45.0	-3.5	-1.9
J. T.....	37	43.6	40.6	42.2	-3.0	-1.4
R. D.....	37	49.0	45.6	47.2	-2.4	-1.8
R. D.....	37	49.1	45.3	46.9	-3.8	-2.2
R. D.....	37	49.3	47.3	48.9	-2.0	-0.4
Average...					-2.9	-1.3

the difference between the members of the pair of curves is greater than when equal concentrations of carbonic acid is the abscissa. The difference between the latter pair, however, is significant. In other words, as temperature rises there is a slight but definite reduction in the buffering power of the blood for any given concentration of carbonic acid.

In view of the parallel trends of both  $\text{CO}_2$ -solubility and available base, it may be predicted that *in vitro* with rising temperatures the bicarbonate-carbonic acid ratio, and hence  $p\text{H}$ , will undergo minimal change at constant  $p\text{CO}_2$ . This prediction is supported by data presented in figure 2b. It so happens that at the physiological range of 30 to 40 mm. Hg of  $\text{CO}_2$  at  $40.5^\circ\text{C}$ , the bicarbonate-carbonic acid ratio remains almost unchanged, so that the temperature effect on  $p\text{H}$ , is merely numerically equal to the small variation of 0.02 which  $p\text{K}'$  undergoes at this temperature. On the other hand, if  $p\text{H}$ , at the two temperatures are compared at the same carbonic acid concentration

(fig. 2a), the bicarbonate-carbonic acid ratio does decrease and the  $pH_s$  falls measurably at  $40.5^\circ\text{C}$ .

*Oxygen dissociation curve.* In 10 experiments performed at normal body temperature, the data collected from all tonometer points relating oxygen

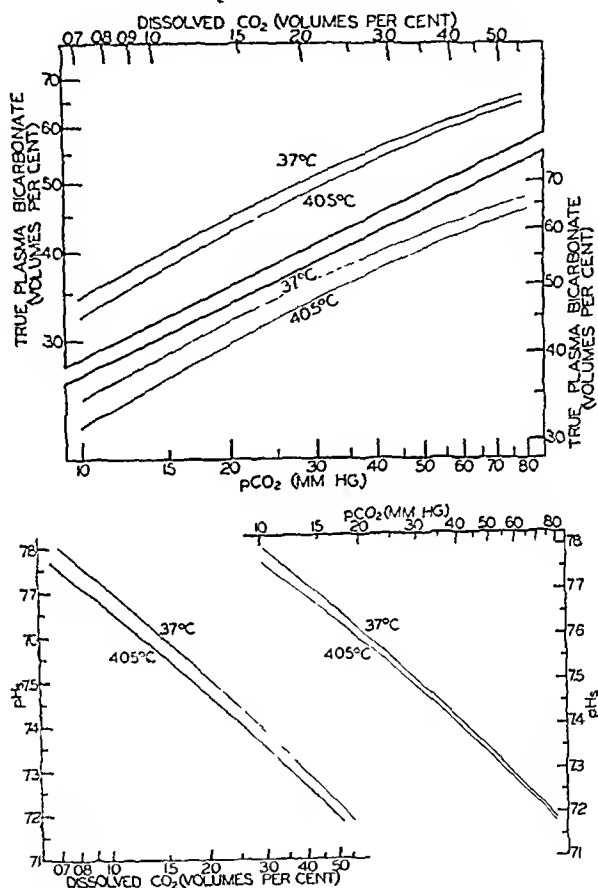


Fig. 1 (upper). EFFECT OF TEMPERATURE on the  $\text{CO}_2$  dissociation curve of true plasma (av. of two normal bloods). a) bottom: plasma bicarbonate plotted against  $p\text{CO}_2$ ; b) top: plotted against carbonic acid concentration (dissolved  $\text{CO}_2$ ).

Fig. 2 (lower). EFFECT OF TEMPERATURE on  $pH$  of the serum (av. of two normal bloods). a) left: related to carbonic acid concentration (dissolved  $\text{CO}_2$ ); b) right: related to  $p\text{CO}_2$ .

saturation and tension, were adjusted to  $pH_s$  7.40 and figure 3 constructed by drawing a best line through them. Similarly, at the range of fever employed ( $40.1$ – $41.2^\circ\text{C}$ .) all data derived from 18 experiments were converted to the same  $pH_s$  and plotted as shown in figure 4. A comparison of our curve at  $37^\circ\text{C}$ . with the standard curve shows a slight displacement of the former to the left

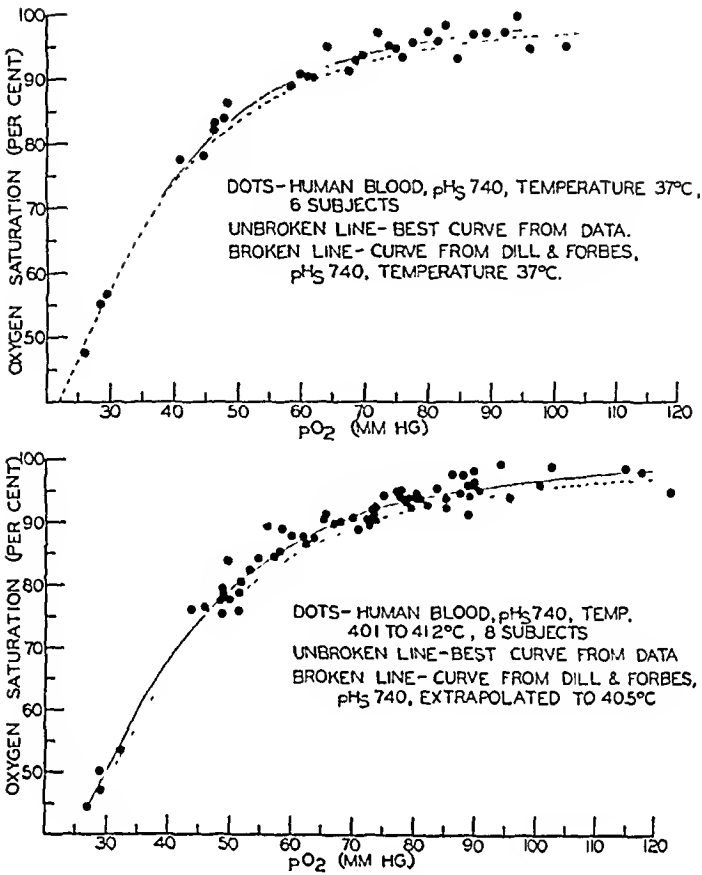


Fig. 3 (upper). OXYGEN DISSOCIATION CURVE of human blood at normal body temperature: measured tonometer points from 10 experiments on 6 subjects, best curve through these points and standard curve from the literature.

Fig. 4 (lower). OXYGEN DISSOCIATION CURVE of human blood at elevated body temperature: measured tonometer points in 15 experiments on 8 subjects, best curve through these points and curve extrapolated from the literature.

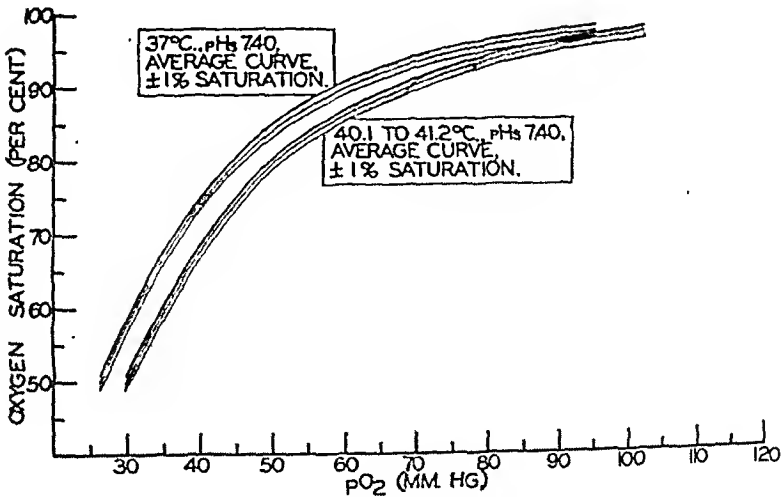


Fig. 5. COMPARISON OF OXYGEN DISSOCIATION CURVES of human blood at normal and elevated body temperatures.

above the range of 80 per cent saturation. The same is true of our fever curve in relation to the one at 40.5°C. calculated from the data of Dill and Forbes (1). To demonstrate the shift to the right with elevated temperature, figure 5 is presented. At a given oxygen saturation the increment of  $pO_2$  with rise in temperature from 37°C. to an average of 40.6°C. is about 13 per cent, which value compares favorably with one of 16 per cent based on the findings of the above-mentioned authors. These results are summarized in table 2.

TABLE 2  
Oxygen Dissociation Curves at  $pH = 7.40$

SATURATION	FOUND $pO_2$ (MM. Hg)		$\Delta$ (% OF 37°)	$pO_2$ (MM. Hg) DILL & FORBES	
	37°	40.1-41.2°		37°	40.5° <sup>1</sup>
%					
50	26.3	29.8	+13	26.3	30.8
60	31.1	35.2	+13	31.1	36.4
70	37.0	41.5	+12	36.1	42.3
80	45.0	50.3	+12	45.7	53.5
85	51.0	57.5	+13	51.7	60.5
90	59.5	67.0	+13	61.4	71.8
94	70.4	80.0	+14	75.0	87.8
96	80.0	89.0	+11	87.7	102.6
98	94.5	102.0	+8	113.0	132.2

<sup>1</sup> Calculated from data  $\Delta$  (%) = 16.

### Physiological Changes

The unsedated group displayed a well-marked uncompensated alkalosis presumably due to an increase in ventilation induced by hyperthermia. This finding agrees with most of the previous reports. Table 3 presents the data on  $pH_s$  and  $pCO_2$  of the blood, the latter values derived from the usual tonometer technique and the direct aerotonometer method. The two methods are in satisfactory agreement. One subject (RC), in spite of a low  $CO_2$ , showed an increment of only 0.02 in  $pH_s$  with fever, a result which may be explained by the rather sharp drop in alkali reserve (6.9 volume per cent), thus compensating for a  $CO_2$  deficit due to hyperventilation (table 4). This decrease in alkali reserve is too large to be explained on the basis of lowered buffering power due to temperature alone. Physiological mechanisms resulting in elimination of base probably were operative. The rest of the subjects showed small changes in alkali reserve, all but one in a positive direction, a trend indicating a concentration of blood proteins including hemoglobin. This is substantiated by the rise in oxygen capacity as seen in table 4. The overall effects of hyperthermia upon alkali reserve are, therefore, unpredictable, being the resultant of many factors. Hemoconcentration of the blood tends to increase available base; the appearance of fixed acids such as lactic

acid (15), renal excretion of base (16) and, as has already been shown, temperature per se, all tend to lower the alkali reserve.

Whereas acid-base equilibrium undergoes marked changes during hyperthermia, the oxygen relationships were found not to be affected at all in the unsedated group. Table 5 presents the observed arterial oxygen tensions

TABLE 3. EFFECT OF PHYSICALLY INDUCED FEVER (40.1-41.2°C.) ON THE CARBON DIOXIDE OF THE ARTERIAL BLOOD<sup>1</sup>

SUBJECT	pCO <sub>2</sub> TONOMETER (mm. Hg)			pCO <sub>2</sub> AEROTONOMETER (mm. Hg)			pH <sub>a</sub>		
	37°	Fever	Δ	37°	Fever	Δ	37°	Fever	Δ
M. K.....	43	38	-5	44	—	—	7.38	7.42	+ .04
R. C.....	41	29	-12	42	33	-9	7.42	7.44	+ .02
E. C.....	41	33	-8	34	32	-2	7.41	7.47	+ .06
R. D.....	44	30	-14	41	29	-12	7.38	7.51	+ .13
L. R.....	39	28	-11	38	27	-11	7.41	7.54	+ .13
G. Q.....	39	33	-6	39	44	+5	7.43	7.49	+ .06
Average.....	41	32	-9	39 <sup>2</sup>	33	-6	7.41	7.48	+ .07

<sup>1</sup> Blood during fever taken after little or no sedation of the patient.

<sup>2</sup> Average of five.

TABLE 4. EFFECT OF PHYSICALLY INDUCED FEVER (40.1-41.2°C.) ON THE ALKALI RESERVE AND HEMOGLOBIN CONCENTRATION OF ARTERIAL BLOOD

SUBJECT	T <sub>60</sub> (OXYGENATED BLOOD) (vol. %)			OXYGEN CAPACITY (vol. %)		
	37°	Fever <sup>1</sup>	Δ	37°	Fever	Δ
M. K.....	47.1	48.0	+0.9	20.8	10.6	-1.2
R. C.....	48.9	42.0	-6.9	20.4	24.8	+4.8
E. G.....	48.7	47.7	-1.0	20.4	21.8	+1.4
R. D.....	49.3	50.9	+1.6	17.9	18.5	+0.6
L. R.....	49.2	50.3	+1.1	16.2	18.7	+2.5
G. Q.....	49.6	49.8	+0.2	17.3	10.4	+2.1
Average...	48.8	48.9	+0.1			+1.7

<sup>1</sup> CO<sub>2</sub> capacity at (H<sub>2</sub>CO<sub>3</sub>) = 2.78 vol. %, which equals (H<sub>2</sub>CO<sub>3</sub>) at 37°C. when pCO<sub>2</sub> = 40 mm. Hg.

found by the two independent techniques and the oxygen saturations. There is no real change in pO<sub>2</sub> with fever, as measured by either method. In one individual (EG), there was an apparent drop of 7 to 9 mm. Hg at the higher temperature. However, on the occasion of another experiment on the same individual at 37°C., arterial pO<sub>2</sub> equaled that found at fever. In another case (GQ), fever caused a rise of 6 mm. This is probably not a significant amount

and is not corroborated by the alternate method. While the tonometer procedure gives a rather low figure for arterial  $pO_2$  in comparison to the aerotonometer technic, for the purpose of this work, not absolute values but differences are to be considered important. The apparent discrepancy is inherent in the tonometer method; the reasons have been discussed by Roughton and coworkers (17). It is to be noted further, that little or no difference in oxygen saturation was observed at the two temperatures employed (table 5).

These observations founded on a study of individual oxygen dissociation curves in unsedated patients fail to support the idea of a state of anoxic anoxia alleged to exist during physical hyperthermia. Turning now to the course of events in sedated patients, again no support is found for the belief in

TABLE 5. EFFECT OF PHYSICALLY INDUCED FEVER ( $40.1-41.2^\circ C$ ) ON THE OXYGEN IN THE ARTERIAL BLOOD<sup>1</sup>

SUBJECT	O <sub>2</sub> SATURATION (PER CENT)			pO <sub>2</sub> TONOMETER (MM. Hg)			pO <sub>2</sub> AEROTONOMETER (MM. Hg)		
	37°	Fever	Δ	37°	Fever	Δ	37°	Fever	Δ
M.K.....	94.8	92.9	-1.9	66	70	+4	98		
R.C.....	96.7	95.6	-1.1	83	82	-1	104	103	-1
E.G.....	93.3	93.8	+0.5	83	74	-9	94	87	-7
R.D.....	96.5	94.3	-2.1	78	81	+3	94	88	-6
L.R.....	93.0	91.0	-2.0	66	69	+3	104	104	0
G.Q.....	93.0	94.1	+1.1	67	73	+6	94	94	0
Average.....	94.5	93.6	-0.9	74	75	+1	98 <sup>2</sup>	95	-3

<sup>1</sup> Blood during fever taken after little or no sedation of the patient.

<sup>2</sup> Average of five.

a generalized anoxia. In contrast to the sedated group, however, a different effect upon the acid-base equilibrium was observed.

Nine experiments performed on patients to whom sedatives were given to control restlessness, exhibited no fall in arterial  $pCO_2$ , nor was there the expected rise in  $pH$ , previously reported during hyperthermia (table 6). These findings are not in accord with the trend frequently mentioned in the literature. If anything, there was an opposite tendency in most and no change in the rest with one exception (MK). This subject, like those in the non-sedated group, exhibited an uncompensated alkalosis; he was a loquacious individual essentially unaffected by the doses of sedative employed. Satisfactory experiments on 2 subjects are available in which direct comparisons can be made among normal body temperature, fever with sedation and fever without sedation (See subjects RC and LR in tables 3, 5 and 6). They clearly show the effect of the medication in counteracting the acapnia ordinarily occurring



during fever. Subject *RC*, however, did not experience a marked change in  $pH_a$  during unsedated fever because of the excessively low alkali reserve, as pointed out before.

In spite of sedation, no appreciable anoxia was encountered in this group; in fact, the average arterial  $pO_2$  was practically identical with that for the unsedated group (table 6). The same applied to the average oxygen saturation. However, the lowest arterial saturation (87 per cent) seen in all experiments, occurred in a patient (*CK*) given sedation. This finding is consistent with the observed arterial  $pO_2$  (63 and 79 mm. Hg, respectively, by the two techniques) and the rather high  $pCO_2$  (50 and 53 mm. Hg, respectively). Omitting this one value from the general average of 92.6, one obtains an aver-

TABLE 6. ARTERIAL BLOOD DURING FEVER IN SEDATED PATIENTS

SUBJECT	$O_2$ SAT.	TONOMETER		AEROTONOMETER		$pH_a$
		$pO_2$	$pCO_2$	$pO_2$	$pCO_2$	
	%	mm. Hg	mm. Hg	mm. Hg	mm. Hg	
<i>M. K.</i>	90.2	66	32			7.48
<i>J. G.</i>	93.9	81	43			7.38
	92.0	65	44	103	30	7.36
	94.0	80	44	86	44	7.34
<i>C. K.</i>	93.6	74	40			7.40
	96.9	95?	43	100	40	7.37
	87.0	63	50	79	53	7.34
<i>R. C.</i>	94.6	88	41	98	48	7.39
<i>L. R.</i>	90.9	71	42	96	53	7.37
Average.....	92.6	76	42	94	45	7.38
Unsedated patients, average.....	93.6	75	32	95	33	7.48

age of 93.2, a figure which compares with saturations found in the control and unsedated patients. Therefore, it may be said that with administration of sedatives only an occasional patient will exhibit a tendency to anoxia, presumably due to respiratory depression.

A graphic summary of the several factors entering into oxygen equilibrium is presented in figure 6. Here oxygen dissociation curves as determined experimentally under the several conditions of temperature alone or with sedation have been plotted for 6 representative individuals. Each curve was adjusted to the  $pH_a$  of the arterial blood. The arterial points (large circles) will be seen to show nearly identical oxygen saturations (ordinates) as well as oxygen tensions (abscissae) under the various conditions of temperature and sedation. As emphasized above, the  $pO_2$  values are better indices of anoxia. The expected relationship between curves at the two temperatures in question is

illustrated and, in addition, in all but one case (*MK*) the characteristic effect of  $pH$  is brought out. Thus, the opposite tendencies of alkalinity and elevated temperature place the oxygen dissociation curve close to the control. It should be emphasized that precise assessment of the curve at its upper end is difficult due to limitations of the method and unexplained variations in the same individual. This has been pointed out by other workers (14, 17). Moreover, part of the interindividual variations may be due to the fact that control and fever bloods were investigated on different days.

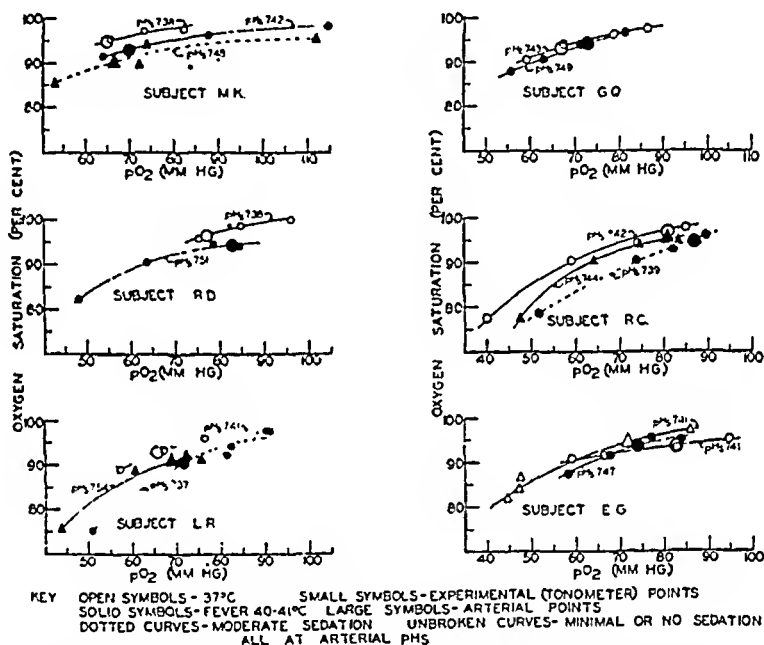


Fig. 6. GRAPHS OF PARTIAL OXYGEN DISSOCIATION CURVES ON 6 subjects under various conditions of temperature and sedation, with positions thereon of arterial points.

## DISCUSSION

A variety of factors contribute to the overall picture of blood gas equilibrium during elevated body temperature, even in simple physically induced fever reported here. It is evident that the changes must be a resultant of physico-chemical changes inherent in temperature itself as well as to physiological adjustments to temperature and other stimuli of many systems directly or indirectly associated. Any over-simplified attempt to explain the low blood CO<sub>2</sub> as a response solely to accumulation of lactic acid with compensatory blowing off of CO<sub>2</sub> (7), to a shift of available base to unavailable protein-bound

base (18), cannot quantitatively account for the observed facts. Although our experiments do not afford a complete insight into events, many of the factors are apparent.

As already mentioned, among the changes dependent on temperature *per se* are solubility of  $\text{CO}_2$  and concentration of available base, which taken together leave  $p_{\text{H}}$  practically normal at the same  $p\text{CO}_2$ . Moreover, while affinity of hemoglobin for oxygen decreases with rise in temperature, provided  $p_{\text{H}}$  remains unaltered, under the prevailing  $p\text{O}_2$  the oxygen saturation will fall by only 2 per cent (table 2). With higher  $p_{\text{H}}$  the affinity for oxygen may remain the same, as illustrated by the oxygen dissociation curves presented in figure 6 (*GQ*, *EG*). If acidosis does supervene, thereby augmenting the temperature effect upon oxygen equilibrium, the resulting oxygen saturation may be expected to fall slightly. When this has occurred, under the conditions of our experiments the levels observed have not suggested oxygen deficit (table 6, *JG*).

The chief physiological response to hyperthermia, viz. the hyperventilation alkalosis that has herein been shown to appear in unsedated individuals, may be attributed to thermal stimulation of the respiratory center leading to low arterial  $p\text{CO}_2$ . Such a mechanism can be postulated upon the work of Heymans and Ladon (19), who observed in cross perfusion experiments in dogs a response of the respiratory center to small changes in temperature of the perfusate. Equally as important in augmenting respiration may be the anxiety and discomfort attendant to the procedure of inducing physical fever itself. Thus, for example, an emotionally unstable individual (*MK*) exhibited acapnia in spite of sedation (table 6). On the other hand, if thermal and emotional stimuli are counteracted by adequate sedation, for example, a moderate acidosis may supervene due to  $\text{CO}_2$  retention.

The hyperventilation alkalosis may in turn be offset by a loss of available base, tending to stabilize the reaction of the blood, as suggested by data on *RC* (table 4). Whether this is an instance of renal excretion of base or neutralization by fixed acids is irrelevant to the proposition that the final outcome depends on the interplay of many trends.

Another factor, in other cases, to be considered in determining  $p_{\text{H}}$ , is the rise in available base, due to the well-known hemoconcentration induced by hyperthermia.

It is logical that hyperventilation should augment the level of alveolar  $p\text{O}_2$  and thence the arterial  $p\text{O}_2$ . However, we did not observe this expected rise. The increase in vapor tension of water between 37 and 40.5°C. would be insufficient to explain this discrepancy between prediction and fact, the dilution effect amounting to less than 2 mm. Hg. Whether the predicted rise is too small to be accurately gauged by the methods employed, or whether diffusion of oxygen is impaired by some change in the alveolar-capillary barrier cannot be said. The finding of pulmonary hemorrhage in dogs by Hartman (8),

would perhaps permit the latter explanation, but the conditions of his experiments were so drastic that they do not apply here. Yet, it may be stated that pathological changes in the lungs of a degree great enough to produce arterial anoxia in dogs, are operative in man only to a small degree under the conditions of our experiments.

Since our evidence does not support the contention that anoxic anoxia is present during fever, it remains to explain the common clinical observations of cyanosis and cerebral disturbances on another basis (20). Although we have noted similar manifestations in some individuals, arterial  $pO_2$  determined in the same individuals did not account for these clinical events. For such a situation to occur in the face of a competent circulation, either the arterial tension must fall to the neighborhood of one half to two thirds of that observed at  $37^\circ C.$ , or the hemoglobin must be transformed to an abnormal pigment. The former explanation is untenable; the latter would seem unlikely from our figures on oxygen capacity. It would seem more likely that cyanosis and cerebral disturbances are caused by slowing of peripheral circulation, probably together with a rise in metabolism due to fever. Stewart has demonstrated a diminution of blood flow in the hands with forced breathing (21); Gibbs *et al.* have noted similar changes in cerebral circulation concomitant with a rise in A-V oxygen difference (22). More specifically, Himwich and his co-workers observed an individual during physical hyperthermia who lapsed into coma when the brain A-V oxygen difference rose to 15.8 volumes per cent (23). Thus, it may be postulated that the hyperventilation associated with fever may account for cyanosis and cerebral disturbances on the basis of an ischemic anoxia rather than an arterial anoxia.

Perhaps a word about the technique of obtaining arterial gas tensions is pertinent. As far as known this is the first investigation reported with simultaneous tonometer and aerotonometer determinations carried out on blood equilibrated at two different temperatures *in vivo*. In 16 experiments in which simultaneous  $pO_2$  data have been obtained, there was an average difference of about 20 mm. Hg regardless of temperature in favor of the aerotonometer, with individual variations of a minimum of 7 and a maximum of 38 mm. Hg (table 5). This average deviation compares favorably with the established value of 20 mm. Hg on the basis of a normal arterial  $pO_2$  of 80 mm. by the indirect and 100 mm. by the direct method. We are aware that our observed difference may be open to question if the corrections applied to aerotonometer results as recommended by the authors are applied.

Our average  $pO_2$  of 74 mm. Hg as found by the classical tonometer method is somewhat lower than accepted standards. This is further reflected in the composite oxygen dissociation curve, based on all our data derived from the tonometer technique, which yields slightly lower values for  $pO_2$  than the standard curve reported from the Fatigue Laboratory. Determination of the upper

portion of the curve by the tonometer method is a somewhat delicate undertaking at best, as pointed out by Roughton and co-workers (17). In addition to the inherent factors which tend to make the apparent oxygen saturation too low, a methodical error of one per cent will yield an error of 5 mm. in  $pO_2$  at the portion of the curve under consideration. Furthermore, inter-individual differences make for further deviations. However, since our composite curve has been established upon a large number of points concentrated in the range above 80 per cent saturation, it is possible that  $pO_2$  as obtained by the tonometer technique may require revision downward in the region mentioned. This is purely an academic point, since in experiments dealing with oxygen tensions, individual dissociation curves must be established and the use of 'standard' curves avoided. The practice of employing such curves has weakened investigations in this regard (10).

#### SUMMARY

1. Changes in blood gas equilibria in response to elevation in temperature were observed in patients undergoing physical hyperthermia at 40.1 to 41.2°C. By means of the classical tonometer technique, alkali reserve and arterial  $pH$ , and  $pCO_2$  were studied at normal and elevated temperatures. In addition, individual oxygen dissociation curves were constructed to compare prevailing arterial oxygen tensions. Independently, direct  $pO_2$  and  $pCO_2$  analyses were also performed by means of the aerotonometer.

2. *Physico-chemical changes.* Studies *in vitro* on the effect of a temperature of 40.5°C. upon alkali reserve agreed with previous workers in that there appeared a slight reduction in  $T_{40}$  of the order of 3.0 volumes per cent for 3.5°C. rise in temperature. When correction was introduced for diminished solubility of the gas at 40.5°C., the decrement amounted to only 1.3 volumes per cent. Thus, the physico-chemical component in the total change is not important. The variation in  $pH$  due to an increment of 3.5°C. as studied *in vitro* was found to amount to less than +0.02 in the range of 20 to 40 mm. Hg of  $pCO_2$ . The finding was explained by the fact that the  $BHCO_3/H_2CO_3$  ratio underwent little or no change due to the parallel influences of reduced alkali reserve and solubility of  $CO_2$ . The oxygen dissociation curve at 40.5°C. was found displaced to the right with an increment in  $pO_2$  of 13 per cent.

3. *Physiological changes.* In patients not receiving sedation an uncompensated hyperventilation alkalosis ensued as reflected in elevated  $pH$ , decreased arterial  $pCO_2$  and minor changes in alkali reserve, usually in a positive direction. In adequately sedated patients  $pH$  was found to be normal or slightly reduced with corresponding changes in arterial  $pCO_2$ .

Arterial  $pO_2$  during body temperatures ranging from 40.1 to 41.2 with or without sedation corresponded to that found at normal body temperature. This finding was derived from data from two independent methods. Oxygen

saturation also remained unaltered. Thus, our experiments failed to confirm the idea of anoxic anoxia during hyperthermia.

4. The effect of various factors upon blood gas equilibria during elevation of body temperatures was discussed and the significance of certain disturbances ensuing thereto was indicated.

We acknowledge gratefully the cooperation of the Neurological Service in allowing us to study patients under their care. We are grateful to the several nurses administering fever therapy at the Columbia-Presbyterian Medical Center for their patient cooperation and whole-hearted assistance.

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# *Measurement of Elastic Properties of Skeletal Muscle in Situ*

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AT PRESENT NO SATISFACTORY METHODS are available for measuring the elastic properties of the muscle as an index of its physical condition. Electromyograms have been used extensively for characterizing the muscle tone and its pathological variations, spasm and paralysis. Frequently, the results obtained have been interpreted in terms of 'tension'. Such an interpretation goes beyond the safely established relationships.

It appeared desirable to develop a method which would characterize quantitatively the condition of muscles in terms directly related to their fundamental physical properties. At the same time the method should be sufficiently simple for use in routine examinations of patients. In this paper an attempt to develop such a method is described, together with an investigation of variables important for standardization of the procedure.

## PRINCIPLES OF ELASTOMETRY

In general, the elastic properties of a body may be determined by either static or dynamic methods. The static methods relate the extent of deformation to the magnitude of a constant external force which is applied to the material (Young's modulus). Methods based on this principle have been repeatedly used for the estimation of muscle 'hardness' (1), but they involve major sources of error. The properties of a viscous-elastic system such as muscle undergo modification by the continued action of the stress. After an initial response this deformation continues to progress so that it is difficult or impossible to define a true end point. Moreover, the prolonged application of an external pressure might provoke interfering proprioceptor reflexes. These difficulties are largely absent in dynamic (ballistic) methods in which the response to a rapid impact is measured. With ballistic methods both deformation and subsequent restoration may be recorded and from these true information is obtained on the viscous and elastic properties of the system.

In industry, elasticity is measured by means of ballistic methods, utilizing mostly the principle of the rebound (2). According to Williams' definition (3, p. 230), "The rebound method acts upon the elastic forms of restitution called into existence when an external force is applied to a body to change the distance between the constituent particles composing the body. If  $R_1$  is the impulse during compression and  $R_2$  during recovery,  $R_2/R_1 = E$  is a constant for any two bodies so long as the impact is not violent enough to produce

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permanent deformation". This approach is an essential part of the method described here. Rebound methods, however, sometimes fail to differentiate accurately between different degrees of hardness and Williams suggested that a study of both the volume (or depth) of the indentation and the rebound might show a better relation to hardness.

A falling pendulum hammer is a convenient ballistic device. The viscous-elastic properties of a test material are expressed by such measurable effects as indentation (deformation) produced by the hammer, the duration of contact ("contact time") between the hammer and the test object and by the relative rebound speed or extent of the rebound of the hammer. The measurement of contact time is technically simple but has not been used for industrial testing of elasticity. In fact, Williams doubts its applicability. The contact time, however, was used to estimate the elastic properties of the biceps muscle in man by Gildemeister (4) and Springer (5).

The contact-time principle is of interest but the procedure used by Gildemeister and Springer was technically faulty. The arm was hung in a sling; as we found in re-investigating their procedure, this arrangement allows the whole arm to make a linear movement in response to the hammer blow which prolongs the contact time.

When a moderate dynamic external force is applied to an imperfectly elastic body like the muscle, the course of deformation (indentation) and restitution is represented by an asymmetrical curve. The degree of asymmetry is an important expression of the physical properties of the test material (muscle), but it cannot be determined from either the contact time or the rebound alone. The combination of contact time and rebound measurement gives more complete information than either method alone.

Steinhausen (6) and Richter (7) made graphical records of the elongation—restitution of isolated muscle during the ballistic impact acting in longitudinal direction. The curves were asymmetrical.

The general limitation in the estimation of muscle elasticity must be recognized. Even in a homogenous substance different elasticity coefficients will be obtained with different types of strain, depending on the direction and speed of application of the external force; these coefficients might be independent of one another. There is a relationship between the elasticity coefficient and hardness, but this relationship is not simple. For this reason, even for measurement of homogenous materials, a relative index for hardness is suggested rather than an absolute coefficient (2). The situation is much more complicated in a heterogenous substance like the skeletal muscle, where an external force produces some dislocation of fibers within the muscle. Furthermore, with intact man, not only the muscle but his overlying skin and subcutaneous tissue contribute to the response. No quantitative allowance can be made at this time for these factors, but it appears that the combined tissue system is dominated by the properties of the underlying muscle.

#### METHOD

The present method provides for the measurement of both contact time and rebound with a ballistic elastometer. The essential apparatus consists of a suspension device from which a pendulum hammer may be released to strike the test object (muscle) at a right angle to its surface, a freely suspended contact plate which just touches the surface of the test object before it is struck by the hammer, devices to record both total contact time between hammer and plate and rebound of the hammer and provisions for the fixation of the test



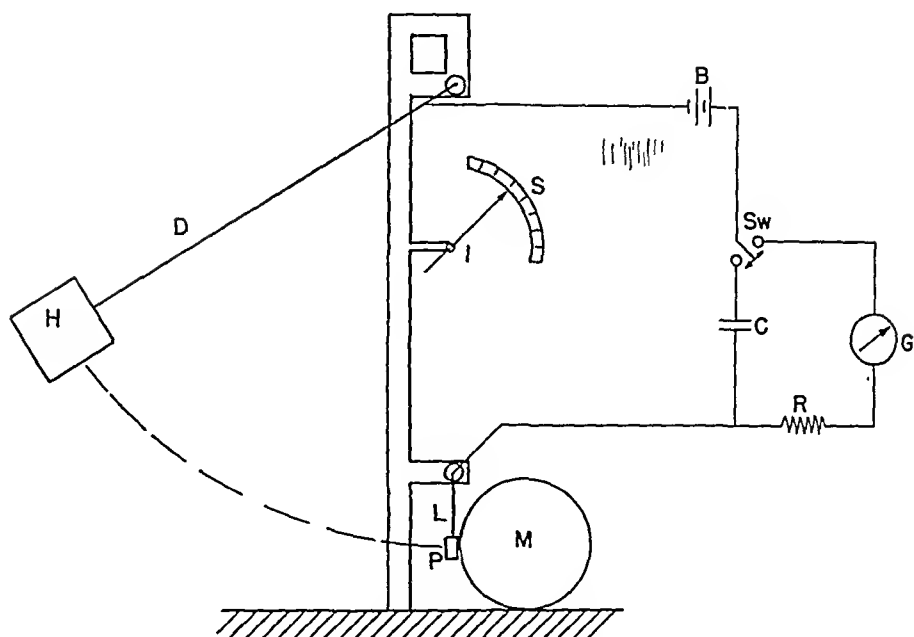


Fig. 1. ELASTOMETER. Schematic diagram. Description s. text.

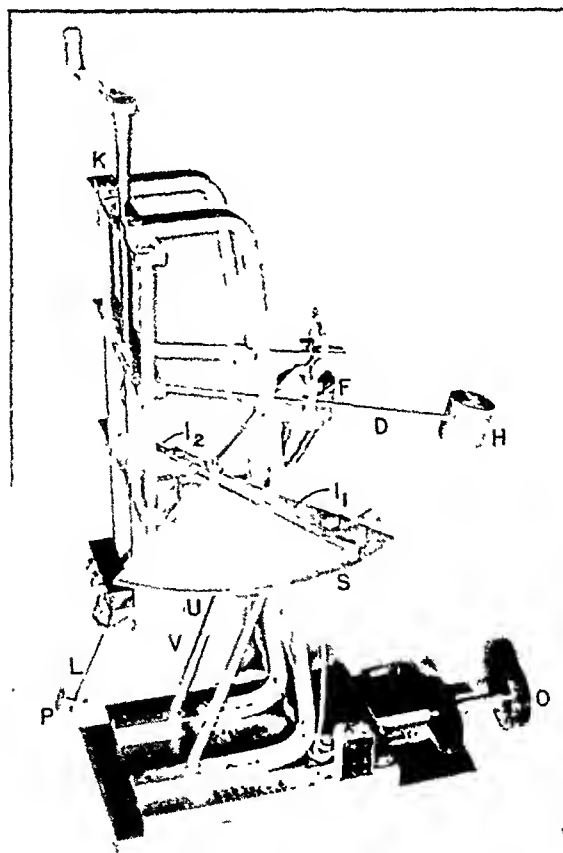


Fig. 2. ELASTOMETER. Description s. text.

object. The central apparatus is shown schematically in figure 1 and photographically in figure 2.

In Gildemeister and Springer's arrangement (4, 5), the contact plate which the falling hammer was to strike was glued to the skin. We found fixation of the metal plate to the skin by means of a thin rubber band was much simpler and gave the same results. However, with both the glue or the rubber fixation great care is necessary to insure that the blow be perpendicular and centered at the midpoint of the area. Even so, a sidewise or torsion displacement of the plate could not always be avoided. Any movement of the plate other than perpendicular would affect the results. Therefore, the plate was mounted to a small lever ( $L$ , fig. 1, 2), which assures that the movement pathway of the plate under the impact of the hammer is always the same. Theoretically, the movement of the hammer and the plate it strikes are divergent due to the different radii of levers  $L$  and  $D$ , but practically this is of minor importance because the depth of penetration of the muscle surface is small in proportion to the radius of the lever  $L$ . The lever  $L$  is slightly overbalanced. The plate  $P$  is brought into contact with the muscle surface by means of the micrometer screws  $O$  (horizontal) and  $K$  (vertical), until the lever  $L$  is in the vertical position, indicated by the pointers  $U$  and  $V$ . By means of this arrangement, the lever  $L$  exerts a constant and practically negligible initial pressure on the muscle. The hammer is released by means of a solenoid ( $F$ ) activated through a push button from a switch board.

The total time of contact ( $T$ ) is measured by an apparatus (fig. 1) consisting of a battery ( $B$ ), resistance ( $R$ ), condenser ( $C$ ), and ballistic galvanometer ( $G$ ). The hammer and the contact plate are in series with the battery, the resistance and condenser. As long as hammer and plate are in contact, the condenser is charged by the battery. The increase of the charge is a function of the duration of contact. The charge is then measured by discharging the condenser through the galvanometer. The details of the electrical circuit will be published elsewhere. The deflection from a standard charge was so calibrated that each division of the scale going from 0 to 100 is equivalent to  $1/1000$  second. Other ranges were provided but are rarely needed in elastometry. The absolute accuracy in reading the scale is about  $\pm 0.25$  scale units.

The rebound coefficient ( $E$ ) is obtained as the ratio of fall height and rebound height, and it is indicated by the pointer  $I$ . This pointer consists of two parts,  $I_1$  and  $I_2$ ;  $I_1$  is freely bent by the falling hammer and returned immediately to its initial position by means of a small spring not visible in the figure. On its way back, the hammer picks up the lever  $I$  as a whole.

The end point of the lever  $I$  moves over a scale ( $S$ ) graduated in terms of the rebound ratio  $E$ . In the present arrangement the scale was calibrated for the hammer falling through  $51^\circ$ . In position zero (shown in fig. 2), the

pointer *I* is a link in the circuit battery-hammer-plate-condenser. As soon as the pointer leaves the zero position the circuit is interrupted and a signal light turned off. Interruption of the circuit immediately after the hammer leaves the muscle prevents further charging of the condenser in repeated contacts.

The operation of the elastometer is simple. After the adjustment of the position of the test object, e.g. the arm for study of the biceps, the operator releases the hammer by remote control. The battery-hammer-plate circuit is connected with the condenser, the switch (*Sw*) being placed in the position 'charge'. After the impact, the switch is turned to position 'discharge' and the deflection of the galvanometer is read. Then the reading of the rebound scale is taken, and the elastometer is prepared for the next impact, i.e. the

TABLE 1. VARIABLES

HAMMER WT., GM.	26.0	51.5		107.0
	Position I	Position II	Position III	Position IV
Fall ht. of hammer, as angle from vertical..	96°	80°	51°	17.5°
Diameter of contact plate.....	1 <sup>3</sup> / <sub>16</sub> "	<sup>7</sup> / <sub>8</sub> "	<sup>1</sup> / <sub>2</sub> "	<sup>3</sup> / <sub>2</sub> " 1"

hammer is brought into striking position, and the pointer *I* into position zero (fig. 2). The determination of both *T* and *E* can be done easily within a few seconds.

This technique was developed and studied systematically by varying the following items: fall height, hammer weight and area and shape of the contact plate (table 1).

Most of the measurements reported here were performed with the contact plate on the belly of the right flexor carpi ulnaris. We are aware that not only this muscle is involved but the whole flexor group of the ulnar region, probably including the flexor digitorum sublimis, and, to a lesser degree, flexor digitorum profundus. For the sake of brevity the term 'flexor ulnaris group' was used in the tables and the discussion.

RESULTS

*Accuracy of the Method.* Simultaneously with the measurement of contact time *T* and rebound ratio *E*, records with a high-speed photokymograph (film speed of 80 cm/sec.) were made of the lever to which the contact plate is attached. For this purpose, a light wooden arm was mounted on the lever *L*, enlarging the amplitude of its movements; in control experiments it was shown that this did not change the *T* or *E* readings. Fifty-two experiments were performed with different hammer weights, different fall heights of the

hammer, two different subjects, in relaxed condition and under tension, as well as with rubber under compression and extension strain. The agreement between the values of  $T$  obtained electrically and photographically was satisfactory under all these variations. Out of the 52 experiments, the values were within  $\pm 0.002$  second in 43 experiments and within  $\pm 0.003$  second in 51 experiments. Only in one experiment a slightly larger difference (0.005 sec.) was obtained.

The differences were not affected by variation of hammer weight, fall height and muscle tension. There was no systematic trend; in about half of the experiments the electrically measured times, in the other the graphically determined times, were slightly higher, so that the average difference is close to zero.

The rebound measurements of  $E$  and the values calculated from the photographic curves were also in satisfactory agreement. The experiments were carried out only in hammer-position *III*, since the  $E$  scale was calculated for the fall height of  $51^\circ$ . A total of 68 experiments were made on 3 subjects with three different hammer weights, in both the relaxed condition and under tension. In only five experiments with the muscles under tension was the difference of the ratios greater than 0.05. These control experiments indicate that the electrical measurement of  $T$ , as well as the mechanical measurement of the rebound coefficient  $E$ , is satisfactory as far as the technical accuracy is concerned.

The contact time  $T$  can accurately reflect the properties of the muscle only if the contact time between the hammer and the rigid metal strike plate is small as compared to the contact time between the hammer and the metal plate placed on the muscle. Control experiments were performed with brass and steel hammers, striking brass or steel bars in rigid fixation. For these control experiments the same flat surface of the hammer was used as in the muscle experiments; the flat surface is not most suitable for determinations of metal elasticity but the experiments were planned merely as a control for our arrangement. The contact time hammer-metal plate alone is in the order of 0.2 to 0.5  $\sigma$ , while the contact time for the hammer-metal plate-muscle is in the order of 50 to 70  $\sigma$  in relaxation; i.e. the contact time hammer-metal plate is relatively short. The expected differences between steel and brass were obtained, but are not discussed here since they are irrelevant for the study of muscle elasticity.

A high degree of agreement between repeated readings in the same experiment was obtained; the data will be reported in a subsequent communication together with values on inter-individual and day-to-day variability. The differences between readings repeated during the same experiment were in the order of  $\pm 1.0 \times 10^{-4}$  second for  $T$  and of  $\pm 0.01$  for  $E$ . The sensitivity of the method is satisfactory for recording changes produced by small amounts

of tension. In fact, the sensitivity is such that in obtaining basal values precautions have to be taken to assure complete relaxation.

*Effect of Hammer Weight.* Experiments were performed with three different hammer weights: 107, 51.5 and 26.0 gm. In each of the three series of experiments, two hammer weights were compared (table 2). It can be seen that the contact time ( $T$ ) for a given condition of the muscle increased in proportion to the square root of the hammer weight. In control experiments on neoprene rubber (6 x 2 x 2 in.) both  $T$  and  $E$  increased with the hammer weight at all sizes of the contact plate (table 3).

TABLE 2. EFFECT OF HAMMER WEIGHT (M) ON CONTACT TIME (T), IN 1/1000 SECOND (AVERAGE VALUES; FLEXOR ULNARIS GROUP) PLATE DIAM.  $\frac{1}{2}$  IN.

NO. OF SUBJECTS	NO. OF EXPTS.	REPEATS IN EACH EXP.	CONDITION	M 26 GM.		M 51.5 GM.		M 107 GM.	
				$T$	$\frac{T}{\sqrt{M}}$	$T$	$\frac{T}{\sqrt{M}}$	$T$	$\frac{T}{\sqrt{M}}$
3	10	5	Relaxed	22.9	4.5			47.4	4.6
12	12	10	Relaxed			36.6	5.1	53.0	5.2
12	12	10	Max. volunt. tension			13.8	1.9	19.9	2.0

TABLE 3. EFFECT OF AREA OF CONTACT PLATE ON CONTACT TIME (T), IN 1/1000 SECOND AND REBOUND (E) FOR NEOPRENE RUBBER. FALL HEIGHT 51°

HAMMER WT., GM.	PLATE DIAM., IN.	T	E
107	$\frac{1}{2}$	6.9	.30
51.5	$\frac{1}{2}$	5.3	.27
26.0	$\frac{1}{2}$	3.9	.21
107	$\frac{3}{8}$	8.7	.39
51.5	$\frac{3}{8}$	6.2	.37
26.0	$\frac{3}{8}$	4.5	.27
107	$\frac{3}{16}$	12.5	.45
51.5	$\frac{3}{16}$	7.6	.37
26.0	$\frac{3}{16}$	5.5	.33

*Effect of the Size of the Contact Plate.* In experiments on neoprene rubber (table 3) both  $T$  and  $E$  increase as the area of the contact plate decreases. The effect of the size of the contact plate was also tested in 2 subjects, using two different hammer weights (26 and 107 gm.) both in the relaxed condition and under tension. The measurements were performed on the flexor ulnar group. Since the results with both hammer weights were similar, only those obtained with the 107-gm. hammer are included in table 4. The results are essentially the same as obtained for neoprene rubber, except that the changes of  $T$  are less uniform in the muscle. We chose one-half inch as the standard diameter for the plate as being most suitable for general purposes. Control

experiments were also made with spherical contact surfaces both for rubber and muscle, but they do not seem to have any particular advantage.

*Effect of Fall Height.* The scale for the rebound ratio was calculated for 51° fall height but it was possible to use photographic records for calculating the rebound for other fall heights. Results obtained on neoprene rubber with three hammer weights and three contact areas for the fall height of 51° and

TABLE 4. CONTACT TIME (T) AND REBOUND (E) WITH DIFFERENT CONTACT PLATES.  
HAMMER WEIGHT 107 GM. POSITION III. RIGHT FLEXOR ULNARIS GROUP

SUBJECT	DIAMETER OF PLATE IN.	RELAXATION		TENSION	
		T	E	T	E
W. C.	1	39	.29	10	.32
	$\frac{3}{4}$	45	.30	12	.38
	$\frac{1}{2}$	45	.305	14	.42
	$\frac{3}{8}$	43	.34	13.5	.45
C. P.	1	51	.235	12	.36
	$\frac{1}{4}$	51	.28	13	.39
	$\frac{1}{2}$	46	.285	13	.43
	$\frac{3}{4}$	48	.295	14	.45
	$\frac{5}{8}$				

TABLE 5. EFFECT OF FALL HEIGHT ON CONTACT TIME (T), IN 1/1000 SECOND  
NEOPRENE RUBBER

HAMMER WT., GM.	CONTACT PLATE, IN	FALL HEIGHT	
		51°	96°
107	$\frac{1}{2}$	6.9	6.8
51.5	$\frac{1}{2}$	5.3	5.0
26.0	$\frac{1}{2}$	3.8	3.7
107	$\frac{3}{8}$	8.7	8.7
51.5	$\frac{3}{8}$	6.2	6.0
26.0	$\frac{3}{8}$	4.5	4.5
107	$\frac{1}{4}$	12.5	13.0
51.5	$\frac{1}{4}$	7.6	7.9
26	$\frac{1}{4}$	5.5	5.4

96° are given in table 5. The contact times were essentially identical for all conditions investigated at these two fall heights.

The same is also true for the relaxed muscle (table 6). However, the contact time decreased at the fall height of 17.5°, possibly because of the interference by skin elasticity. The photographic records show only a very slight indentation at this fall height. There is no evidence of interference by skin elasticity at fall heights between 51° and 96°. Obviously, a fall height of 17.5° is not suitable for testing muscle elasticity. For the same reason the hammer weight of 107 gm. is preferable to the hammer weight of 26 gm.

*Effect of Skin Thickness.* From the investigation of the effect of the fall

height it was concluded that skin elasticity would interfere with the measurement of muscle properties only at very small fall heights. However, it was desirable to have direct evidence concerning the possible effect of the skin. The gastrocnemius areas of 10 subjects were investigated on three different days, with five repeat readings in each experiment. The thickness of the skin fold was measured by means of a caliper. Figure 3 shows the lack of significant correlation between thickness of the skin and contact time or rebound. The range of the skin thickness as well as that of the contact time was large enough for demonstration of a correlation. The results in figure 3 refer to relaxed condition at a flexion angle of  $30^\circ$  at the knee and of  $105^\circ$  at the ankle, but a lack of correlation was also observed in other positions. This does not prove that skin elasticity has no effect on the measurements, but it does show

TABLE 6. EFFECT OF FALL HEIGHT ON CONTACT TIME (T) AND REBOUND (E). FLEXOR ULNARIS GROUP IN RELAXED CONDITION

SUBJECT	HAMMER WT., GM.	FALL HEIGHT	T	E
A. B.	107	$96^\circ$	51	.20
	107	$51^\circ$	51	.24
	107	$17.5^\circ$	42	.33
	26	$96^\circ$	30	.16
	26	$51^\circ$	28	.21
	26	$17.5^\circ$	17	.33
C. P.	107	$96^\circ$	50	.21
	107	$51^\circ$	49	.25
	26	$96^\circ$	33	.20
	26	$51^\circ$	30	.18

that a rather large variation of skin thickness is not important enough to affect systematically the interindividual variability.

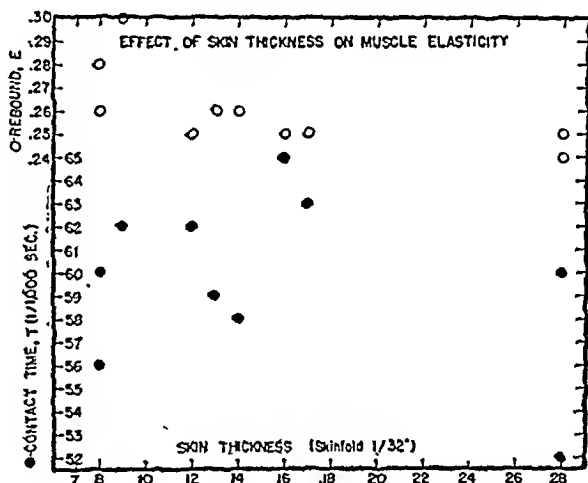
*Effect of Tension.* One of the major objectives of the present method was to provide means for quantitative characterization of the effects of tension. In order to do this it was necessary to study the effect of controlled tension, produced by known loads, on *T* and *E*. This could not be done satisfactorily by using the muscle *in situ* because the production of tension is a complicated mechanism and the tension within the muscle need not be identical with the load applied to the muscle or the external force exerted by the muscle. Therefore, experiments on elastic material subjected to physically defined tensions were performed.

The effect of known load and tension in the longitudinal direction was tested on narrow bands of natural and synthetic rubber. For this purpose, the lever *L* was fixed in vertical position by a support in such a way that it could move only in the direction of the hammer blow. The rubber strip was fastened on two hooks extending horizontally in the plane of the hammer path-

way. One hook was soldered to the end of the lever  $L$ , and the other one to a movable metal rod. The length of the rubber strip was stretched by means of the movable rod to the three lengths corresponding to three loads, as shown in table 7. The absolute values for the two materials are not exactly comparable, because the thickness of the natural and the synthetic rubber pieces were different.

While the contact time decreases with increasing tension in natural as well as synthetic rubber (much more so with natural rubber), the rebound does not change for natural rubber while it increases markedly with increasing tension for the synthetic rubber. In contrast to the results obtained with compression elasticity (see table 5), the contact time increases with increasing fall

Fig. 3. LACK OF SIGNIFICANT CORRELATION between skin thickness (abscissa,  $\frac{1}{32}$  in.) and elastic properties of the muscle (rebound  $E$ , upper part, empty circles; contact time  $T$ , lower part, solid circles).



height. The reason for the discrepancy of the effects of fall height under longitudinal and compression stress might be that in the case of the compression elasticity the elastic force developed in the rubber is proportional to the distance of penetration, while in the case of longitudinal stress the external tension is probably a complicating factor. On the other hand, contact time and rebound decrease with decreasing hammer weight at all tensions in both natural and synthetic rubber, as was the case also for compression stress.

The effect of voluntary tension on muscle elasticity was already indicated in tables 2 and 4; it can be seen that tension produces a pronounced decrease of  $T$  and an increase of  $E$ . This is similar to the response of synthetic rubber and different from the response of natural rubber to tension (table 7) where the decrease of  $T$  was not associated with an increase in  $E$ .

Table 8 shows the effect of the fall height on contact time and rebound for the flexor ulnaris group during maximum voluntary tension. In contrast to the relaxed muscle (table 6),  $T$  is smaller for the fall of  $96^\circ$  while  $E$  is not



changed. This might indicate not only a quantitative but also a qualitative change of the elastic properties of the muscle in tension.

It should be noted that increasing fall height lengthens the contact time of rubber under tension and that this is opposite to the change produced by

TABLE 7. CONTACT TIME (T) AND REBOUND (E) FOR NATURAL AND SYNTHETIC RUBBER ON LONGITUDINAL STRESS

SUBSTANCE	HAMMER WT., GM.	LENGTH, CM.	LOAD	T			E
				Fall Height			51°
				96°	80°	51°	
Natural rubber	107	8.6	50			54	.60
	51.5	8.6	50		38	36	.49
	26	8.6	50	31	29	27	.41
	107	11.5	310		49	39	.60
	51.5	11.5	310	33	29	21	.48
	26	11.5	310	19	17	12	.41
	107	17.5	570	42	37	26	.63
	51.5	17.5	570	24	20	13	.47
	26	17.5	570	11	11	6	.41
Synthetic rubber	107	7.10	100		42	36	.42
	51.5	7.10	100	29	27	23	.34
	26.0	7.10	100	18	16	14	.29
	107	9.5	330	42	39	33	.53
	51.5	9.5	330	27	24	18	.45
	26	9.5	330	15	14	10	.39
	107	11.5	470	37	35	28	.59
	51.5	11.5	470	24	22	16	.52
	26	11.5	470	14	12	9	.42

TABLE 8. EFFECT OF FALL HEIGHT ON CONTACT TIME (T) AND REBOUND (E) IN MAXIMUM VOLUNTARY TENSION. FLEXOR ULNARIS GROUP. HAMMER WEIGHT 107 GM.

SUBJECT	FALL HT.	T	E
A. B.	96°	17.5	33
	51°	23.0	34
C. P.	96°	11	57
	51°	15	58

tension in muscle. This discrepancy might be explained by the different directions (longitudinal and transversal) of the strain in the rubber strip and the muscle or might indicate a fundamental difference in elastic properties between muscle under tension and rubber under tension.

*Differences in Different Regions of Muscles.* Measurements were per-

formed in three different locations on the muscle: the proximal third, belly and distal third. Table 9 shows that the contact time is different in different parts of the same muscle, more so in the flexor ulnaris group than in the biceps. The 2 subjects differ somewhat in the trends. The experiments were undertaken for the limited purpose of standardization of procedure. It appears that the anatomical location for elastometric measurements must be rather well defined and standardized.

*Concept of an Elastic Coefficient and a Damping Constant.* An elasticity coefficient and a damping factor may be calculated from a general equation:

(1)  $M \frac{d^2x}{dt^2} + \mu \frac{dx}{dt} + \alpha x$  where  $M$  is the mass of the hammer weight in gm.,  $x$  the indentation at the time  $t$ ,  $\mu$  the damping factor and  $\alpha$  the elasticity coefficient. Steinhausen (6) and Richter (7) found that  $\alpha$  and  $\mu$  changed under

TABLE 9. CONTACT TIME (T) AND REBOUND (E) IN DIFFERENT PARTS OF THE MUSCLE (AV. VALUES)

SUBJECT	MUSCLE	PROX. THIRD		BELLY		DISTAL THIRD		CONDITION
		T	E	T	E	T	E	
C. P.	Flex. uln.	44	.26	56.5	.25	52	.275	Relax.
	" "	12	.415	15.5	.395			Tension
	Biceps	78	.24	77	.26	64	.26	Relax.
	" "	18	.45	18	.44	19.5	.41	Tension
W. C.	Flex. uln.	43	.23	53	.28	61	.23	Relax.
	" "	12.5	.425	15	.39	18	.37	Tension
	Biceps	70	.295	72	.26	72	.28	Relax.
	" "	31	.40	30	.425	39.5	.355	Tension

experimentally varied conditions of the muscle. The formula they used implies that the same  $\alpha$  and  $\mu$  could be obtained at different hammer weights. However, they did not actually test this assumption.

We calculated  $\alpha$  and  $\mu$  for different hammer weights, fall heights (from photographic records) and contact areas, and found that the  $\alpha$  and  $\mu$  values increased with the hammer weight and also varied with the contact area. This means that  $\alpha$  and  $\mu$  are not independent of the conditions of measurement and, consequently, it is questionable whether for most purposes anything will be gained by calculating  $\alpha$  or  $\mu$  by an equation which is a rough approximation at best.

It is of interest to know whether the determination of  $T$  and  $E$  is useful for characterizing the asymmetry of the deformation curve, which is an important elastic characteristic. We calculated from the experimentally determined contact time and rebound the penetration distance using numerous time segments, on the basis of equation (1) which seems suitable for this pur-

pose. The curves thus obtained were compared with the actual photographic recording as shown in figure 4. It can be seen that the calculated curve fits quite well the actual curve.

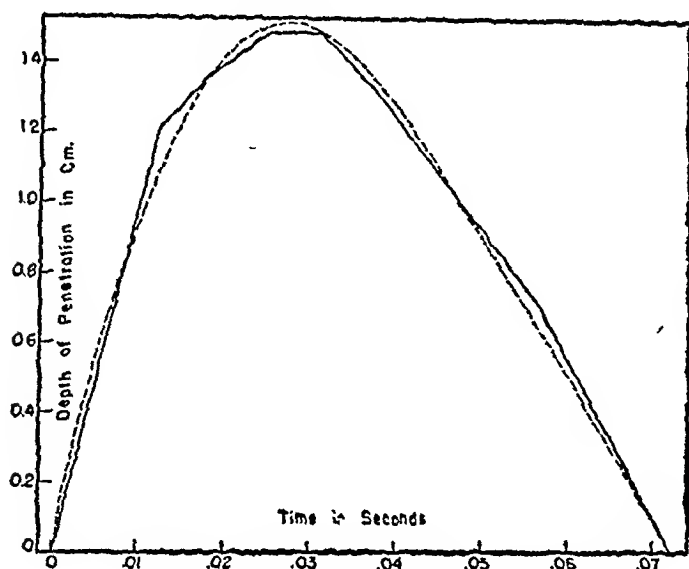


Fig. 4. AGREEMENT BETWEEN CALCULATED DEFORMATION CURVE (broken line) and photographically determined deformation curve (solid line).

#### COMMENT

The model experiments with rubber were performed in order to determine the sensitivity of the method to a known and reproducible external tension, to investigate the effect of some instrumental factors such as fall height and to study the consistency of repeated determinations in an inert material. Longitudinal tension in rubber strips produced clear-cut changes in the elastic properties as recorded by the present method. The changes were different in certain respects from the effects of voluntary tension in muscle. The fact that the method shows differences in the responses of natural and synthetic rubber is encouraging, since it justifies the expectation that it may also differentiate changes in the physical properties of the muscle produced by various pathological changes. This is supported by some evidence, presented in this paper, that the changes produced by maximum voluntary tension are quantitative as well as qualitative.

The present results show that the actual situation is too complicated to calculate a definite elasticity coefficient or damping constant as has been done for the isolated muscle by Steinhausen and by Richter, who used a comparable method. Since it seems impossible, at least at present, to arrive at absolute coefficients of elasticity, it is necessary to standardize the procedure in order to arrive at comparable values, which are exact and reproducible under standard conditions. Such relative standardization has also been accepted in industry for testing the hardness of rubber.

The following standardization for the procedure is recommended: hammer weight 107 gm., contact plate one-half inch in diameter and fall height

51°. The standardization of the size of contact plate and of fall height need not be rigorous; similar values will be obtained with a contact plate 50 per cent larger or smaller, and within a range of fall height between 51° and 96°.

#### SUMMARY

A dynamic method is described for estimation of the elastic properties of skeletal muscles *in situ*. It is based on electrical measurement of the contact time between a hammer and a metal plate in contact with the muscle, and on mechanical measurement of the rebound. The method is simple and the single readings can be made within a matter of seconds. The contact time is probably too short for interference of proprioceptive reflexes. Control experiments with photographic recordings showed that the time as well as rebound measurements are sufficiently accurate. The size of the 'chance' variations in the readings (the error of the method) is small compared to the changes produced by alterations in muscle tension.

Variation of fall height of the hammer, hammer-weight and contact area was investigated in natural and synthetic rubber and in muscle in the relaxed condition and under maximum voluntary tension. Differences in physical properties were revealed between natural and synthetic rubber, between rubber and muscle and between relaxed muscle and muscle under tension. These differences were quantitative as well as qualitative.

The physical situation in the muscle *in situ* is too complicated for calculation of a definite elasticity coefficient or damping constant. On the basis of the experiments with fundamental variables, conditions for standardization of apparatus and procedure are suggested.

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# *Dynamic Features of Human Isolated Voluntary Muscle in Isometric and Free Contractions*

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IN AN EARLIER PAPER (1) we have described the isometric length-tension diagram and certain other features of human isolated voluntary muscle, studied in amputees possessing cineplastic tunnels through various muscles of the upper extremity. The present report<sup>1</sup> represents a continuation of that study.

## MATERIALS AND METHODS

The isometric contractions described in the present paper were recorded with the strain gauge dynamometer described in the previous paper. For the measurement of rates of shortening of muscle under various loads, a light lever, constituting one arm of a resistance bridge, was connected to a cable supporting the load. As the load was lifted, the bridge unbalance was measured by a Heiland type A galvanometer and recorded on a Heiland type SE-301 R-12 oscillograph. Over the range of excursions studied, the bridge unbalance was a linear function of the excursion.

The load-velocity curves described in the present paper are based upon data obtained from the sternal portion of the pectoralis major. Experiments on the biceps brachii and triceps did not yield sufficiently smooth curves to warrant mathematical analysis. Certain data on the latter muscles will, however, be given.

## RESULTS AND DISCUSSION

*Relation between Load and Maximal Velocity in the Afterloaded Muscle.* Every attempt was made to reproduce as closely as possible the experiments made on frog and cat muscle by Fenn and Marsh (2) and on frog muscle by Hill (3). The muscle was initially stretched with a load of 0.32 kg. to a length

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<sup>1</sup> These experiments constitute a portion of the Prosthetic Devices Research Project, College of Engineering, University of California, Berkeley, under contract VAM-21223, National Research Council, Committee on Artificial Limbs. The project was under the general direction of H. D. Eberhart, Associate Professor of Civil Engineering. The research was aided by a Grant from the National Foundation for Infantile Paralysis.

slightly beyond the resting length, all greater loads being supported by a block. The subject was instructed to shorten his muscle as rapidly as possible upon receiving a signal. At least two sets of measurements, in ascending and descending series, were made in each experiment. The maximal force which the muscle could develop at the initial length was determined with the isometric dynamometer.

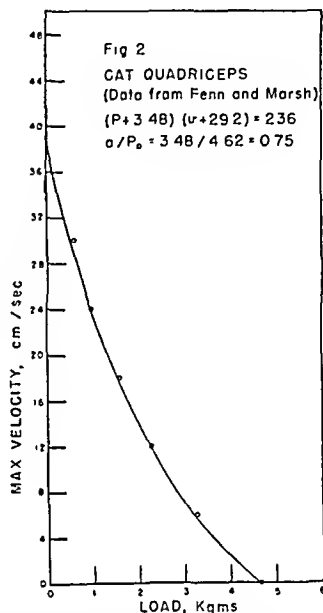
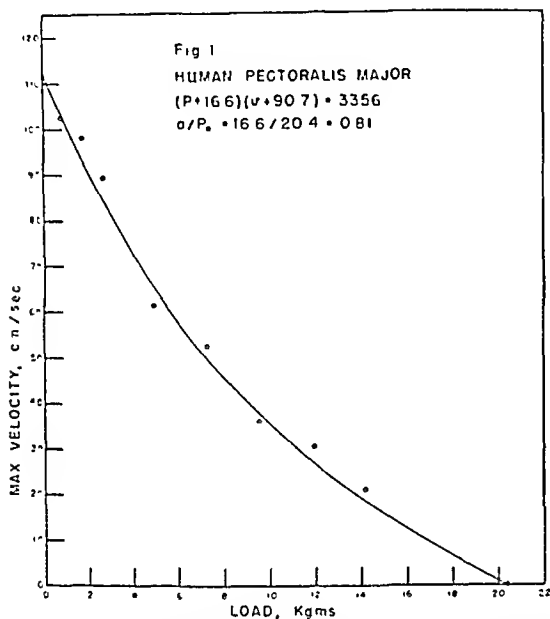


Fig. 1. RELATION BETWEEN LOAD AND MAXIMAL VELOCITY in the human pectoralis major. Circles represent means of two values. The smooth curve is calculated from the equation shown in the figure.

Fig. 2. RELATION BETWEEN LOAD AND MAXIMAL VELOCITY in the cat quadriceps. Circles represent values picked from the curve provided by Fenn and Marsh (2). The value for the isometric tension was determined by extrapolation. The smooth curve is calculated from the equation shown in the figure.

Figure 1 shows the relation between load and maximal velocity in the pectoralis major. Each experimental point, represented by a circle, is the mean of two values. In order to show the variability in the measurements, the data of the experiment are provided in table 1.

Figure 3 is a record of the pectoralis shortening under a minimal load of 0.32 kg. It will be observed that the entire shortening of nearly 9 cm. required only about 0.12 second. The sigmoid character of the curve is quite evident. This is always the case except with very heavy loads, when the curve tends to be flat over a large portion of the excursion. As a consequence of the sigmoid form, the maximal velocity, as measured by the slope of the curve at the point of inflection, ordinarily is much greater than the average velocity.

TABLE 1. RELATION BETWEEN LOAD AND MAXIMAL VELOCITY IN THE AFTER-LOADED PECTORALIS

LOAD	MAX. VILLOCITY	LOAD	MAX. VELOCITY	LOAD	MAX. VELOCITY
kg.	cm/sec.	kg.	cm/sec.	kg.	cm/sec.
0.77	101	11.9	28	7.27	49
1.73	91	14.2	18	4.95	63
2.68	92	20.4 (Isometric)	0	2.68	87
4.95	59	14.2	24	1.73	105
7.27	56	11.9	33	0.77	104
9.59	34	9.59	38		

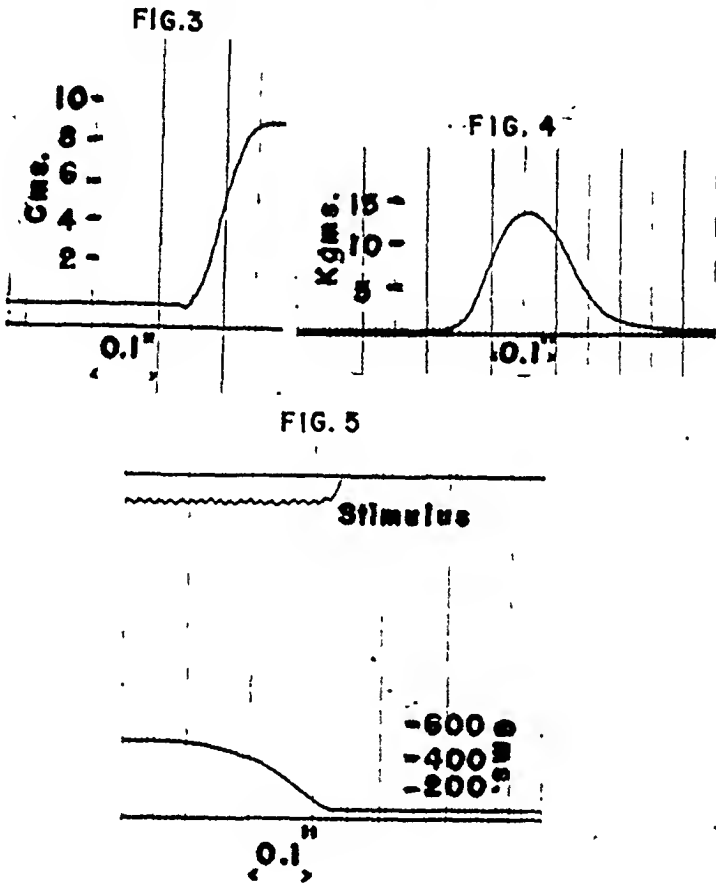


Fig. 3. ORIGINAL RECORD OF HUMAN PECTORALIS SHORTENING under a load of 0.32 kg. The lower line is a reference line for measurement purposes.

Fig. 4. ORIGINAL RECORD OF A MAXIMAL ISOMETRIC CONTRACTION of a human pectoralis, performed as rapidly as possible. The lower line represents zero tension.

Fig. 5. TO BE READ FROM RIGHT TO LEFT. Original record of a maximal isometric tetanic contraction of a frog gastrocnemius. The lower line represents zero tension.

In the present case the maximal velocity is 143 cm/sec., which is approximately twice the average velocity.

Ramsey (4) has elaborated a mathematical treatment of the force-velocity relationship in muscle, based upon the assumption that a muscle shortens at a

rate proportional to the distance to which it still can shorten. Such an assumption cannot be valid, since it is clear that the shortening curve of muscle must start with zero velocity at zero slope (a finite slope would require infinite force) and end at zero velocity. The curve therefore has a point of inflection, and the slope at this point, as already mentioned, represents the maximal velocity. Ramsey bases his assumption on the experimental curves obtained by Fenn and Marsh with frog muscle. A careful examination of these curves, however, shows that they are sigmoid in character, like those obtained in the present study. It appears improbable that any assumption like that of Ramsey, however attractive in its simplicity it may be, will be adequate to describe the behavior of the complicated chemical system found in muscle.

Hill (3) found that plotting  $(P + a)v$  against  $P$  for frog sartorius yielded a straight line,  $P$  being load,  $v$  'velocity,' and  $a$  the shortening heat per unit shortening, having the dimensions of force. By a simple mathematical transformation, this leads to  $(P + a)(v + b) = (P_0 + a)b = \text{constant}$ , where  $P_0$  is the isometric tension at initial length, and  $b$  is a constant, having the dimensions of velocity. The last equation represents a hyperbola. Fenn (5) has discussed this equation at some length and has pointed out how insensitive the curve is to relatively large variations in the values of the constants, a fact which we have abundantly verified.

There is no doubt that many data relating force and maximal velocity, for a wide variety of muscles, may be fitted with an equation of the form  $(P + a)(v + b) = \text{constant}$ . In figure 1 we have drawn the curve represented by the equation  $(P + 16.6)(v + 90.7) = 3356$ , which adequately fits the experimental points. The value of  $a/P_0 = 0.81$ , however, is far from the value 0.25 supposed by Hill to represent a fundamental constant of muscle, even in human voluntary contractions (6). In another experiment on a different pectoralis,  $a/P_0$  had the value 0.39. A close examination of Hill's data does not adequately support the claim that  $a/P_0$  is constant even for a single type of muscle under the highly restricted conditions of Hill's experiments.

Fenn and Marsh (2) fortunately have provided data on the quadriceps and gastrocnemius of the cat. We have calculated, for their experiment number 7a on the quadriceps, the curve shown in figure 2, which yields a value of  $a/P_0 = 0.75$ . Another of their experiments (no. 3 on the gastrocnemius) yields a value for  $a/P_0 = 0.44$ . It is clear, therefore, that the value of  $a/P_0$  is subject to wide variation. Indeed, there is no theoretical reason to expect otherwise.

The fact that many data relating force to maximal velocity may be fitted with Hill's equation is of no real significance. French curves of a wide variety of forms may be equally well fitted. With the use of this equation, and certain assumptions concerning the elastic component of muscle and the rapidity of attainment of maximal (?) velocity with a given load, Hill has been able to



derive equations which yield curves *grossly* resembling the form of the isometric contraction in certain muscles and the form of certain curves obtained in the Levin-Wyman experiment (7). It should be emphasized, however, that Hill's observations were made under the very limited condition that only a small region of the length-tension diagram was involved. It is hazardous to generalize these observations by assuming that the ratio  $a/P_0$  remains constant under all conditions and particularly to assume that this ratio represents a fundamental constant of muscle behavior. As a matter of fact, Katz' studies (8) underscore this need for caution. Katz worked under the same conditions as those obtaining in Hill's experiments and, using the same method of evaluating the velocity of contraction, found that the velocity for a load greater than  $P_0$  was not in agreement with that predicted by the Hill equation. We conclude that the Hill equation cannot be considered an exact equation, and that it is a

TABLE 2. FREE CONTRACTIONS IN HUMAN MUSCLE, STARTING AT NEAR REST LENGTH

MUSCLE	MAX. VELOCITY	MAX. EXCURSION	MIN. TIME FOR TOTAL SHORTENING
	<i>cm/sec.</i>	<i>cm.</i>	<i>sec.</i>
Pectoralis.....	145	8.7	0.10
Biceps.....	92.5	8.4	0.17
Triceps.....	55	4.0	<0.10

satisfactory empirical equation only if it is recognized that the values of the 'constants' vary from one experiment to another.

We propose, in a later paper, to examine critically Hill's treatment of the load-velocity relationship, and to offer a new treatment based upon the known physics and chemistry of muscle.

*Some Basic Data on Free Contractions.* Table 2 provides data on free contractions of the sternal portion of the pectoralis major, the biceps brachii and the triceps. The muscles were minimally loaded with 0.32 kg. and therefore were slightly beyond resting length at the beginning of the contraction.

There is a rough correspondence between length of muscle fiber and maximal velocity. Unfortunately, we do not know very accurately the fiber lengths in the muscles of our subjects, but E. Weber (9) gives the following average figures:<sup>2</sup> sternal portion of pectoralis major, 14.74 cm.; biceps brachii, 12.8 cm.; triceps (long head), 7.74 cm.; triceps (short head), 5.83 cm. It so happened that the maximal isometric tensions at resting length of the muscles in table 2 were nearly equal, so we should expect the maximal velocities to be

<sup>2</sup> It may be objected that Weber's figures are greater than those obtained by certain recent workers, and that Weber probably was measuring bundle lengths rather than fiber lengths. Aside from the fact that there is no real agreement among histologists as to fiber lengths in human muscles, it should be noted that from the functional standpoint it makes no difference whether a fiber is a single long structure or is composed of shorter sections linked end to end.

proportional to fiber length. Maximal excursion also is roughly proportional to fiber length. The ratios of excursion to fiber length are 0.59, 0.65 and 0.59, respectively, for the muscles of table 2. These values are in excellent agreement with the figure 0.6 found by Zchakaia (10) for cat sartorius under comparable experimental conditions. As Zchakaia showed, however, the ratio would be different for muscles whose fibers are not parallel or approximately parallel. Haines (11) found that the maximal excursion of straight-fibered muscles in the intact human body averaged 57 per cent of the maximal extended length.

*Isometric Contraction.* Figure 4 shows a typical record of a maximal isometric contraction of the pectoralis, performed as rapidly as possible. It will be observed that full tension was developed in about 0.12 second. With this record may be compared that of figure 5, which shows a maximal tetanic isometric contraction of a frog gastrocnemius at 20°C., also recorded with a strain gauge. Here the time required for the attainment of full tension was over 0.2 second. It is well known that the time required for development of maximal tension, and the amount of tension, in experiments on isolated muscle, depend on both the rate and the duration of the stimulation. We have found, however, that a maximal effort in our subjects leads to the same, or practically the same tension, regardless of how rapidly the effort is made. In other words, it appears that in a maximal voluntary isometric contraction the muscle is 'tetanized' as much as it voluntarily can be, regardless of speed of effort. The muscle is protected, so to speak, against the possibility of development of the higher tensions producible by artificial stimulation.

*Absolute Muscle Force.* Many authors have expressed the force developed by a muscle in terms of the ratio of isometric force to physiological cross-section. The latter is obtained by dividing the volume of the muscle by the length. It is clear, however, as Haxton (12) has pointed out, that this 'absolute muscle force' does not have much meaning unless the conditions under which the force is measured are rigidly specified, since the force developed depends upon the length of the muscle. In a very careful study of the human ankle flexors, in which the length of the muscles at mid-position was used, and corrections made for obliquity of the muscle fibers, Haxton found an average value of 3.9 kg/sq. cm.

Table 3 provides data on the sternal portion of the pectoralis major, the biceps brachii, and the triceps, as observed in 2 of our subjects. The forces given are the maximal isometric developed tensions. The values of the cross-sections are taken from Weber (9). These cross-sections, judging from the work of Haxton (12), are probably too low. It is also probable that the values of the forces observed in our subjects are lower than those occurring in normal subjects.

Fenn and Marsh (2) provide data on cat muscle. Unfortunately, we

cannot be sure that the muscles were studied under conditions strictly equivalent to those of table 3. Calculating the cross-sections from the given lengths and weights of the muscles, we arrive at an average of 1.225 kg/sq. cm. for the cat quadriceps, and 6.356 kg/sq. cm. for the cat gastrocnemius. We have found, for the gastrocnemius and the anterior tibial of the rat, values ranging from 0.74 to 1.24 kg/sq. cm. It should be noted that the tensions developed in voluntary contractions are certainly less than those which would be developed with maximal artificial stimulation. The variability in the various figures quoted in this section therefore makes it unlikely that the value of the absolute muscle force has any general usefulness. It would be hazardous, at least, to apply the figure for one muscle to any other muscle.

*Power.* Since the curve relating load and maximal velocity can be fitted by an equation of the form  $(P + a)(v + b) = \text{constant}$ , it follows, as Hill (3)

TABLE 3. MAXIMAL DEVELOPED FORCE IN HUMAN ISOLATED MUSCLE

MUSCLE	CROSS-SECTION	MAX. DEVELOPED FORCE	KG. SQ. CM.
	sq. cm.	kg.	
Pectoralis.....	12.8	20.9	1.63
Biceps.....	9.15	21.8	2.38
Triceps.....	15.98	20.9	1.31

has shown, that the load at which maximal power is developed may be determined by differentiating the product  $Pv$  with respect to  $P$ , and setting  $d(Pv)/dP = 0$ . This leads to the result that the power is maximal when  $\frac{P}{P_0} = \frac{a}{P} \left( \sqrt{1 + \frac{P_0}{a}} - 1 \right)$ , where  $\frac{P}{P_0}$  is a certain fraction of the isometric tension. This fraction is very insensitive to large changes in the value of  $a/P_0$ , varying only from 0.23 to 0.41 as  $a/P_0$  varies from 0.1 to 1.0. It follows, therefore, that an isolated muscle will develop maximal power when lifting a load equal to about one quarter to two fifths of the maximal isometric tension the muscle can develop at initial length. This fact is not of great interest, however, since the maximal velocity, and therefore the maximal power, is only momentarily maintained.

Using the value  $a/P_0 = 0.81$  for the muscle of figure 1, we find that maximal power occurs when the load is 8.36 kg., corresponding to a velocity of 42 cm/sec. This leads to a value for the maximal power of 34.5 watts or 0.046 horse-power.

SUMMARY

Voluntary contractions of the human pectoralis major, biceps brachii and triceps muscles were studied under isometric and isotonic conditions, in sub-

jects having cineplastic muscle tunnels. The curve relating load and maximal velocity could be fitted by an equation of the form  $(P + a)(v + b) = \text{constant}$ , as found by Hill for frog muscle. The constants of the equation, however, are different from those obtaining in frog muscle. Load-velocity curves for other types of mammalian muscle, as obtained by other investigators, are shown also to yield values of the constants not in agreement with those for frog muscle. Certain criticisms are offered of the treatment of the load-velocity relationship as presented by Ramsey and by Hill. Some basic data on free contractions of human muscles are provided. It is shown that there is a rough proportionality between the velocity and fiber (or bundle) length, and between excursion and fiber (or bundle) length.

The form of the isometric contraction is described. Evidence is provided that the value of the 'absolute muscle force' varies from one muscle to another, under conditions of both voluntary and artificial stimulation. The power developed by a muscle is briefly discussed, in terms of the Hill equation. The maximal power developed by the isolated sternal portion of the human pectoralis major is of the order of 35 watts.

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# *Electrokymographic Studies of the Ventricular Isometric Relaxation Phase of the Cardiac Cycle in Man*

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IT HAS BEEN PREVIOUSLY SUGGESTED that the duration of the ventricular isometric relaxation phase of the cardiac cycle might provide valuable information pertaining to the condition of the ventricular muscle. Wiggers (1), emphasized that this phase provides "an index to the relaxation process". Burstein (2), suggested that the "functional condition" of the ventricular muscle might well be indicated by the duration of the isometric relaxation phase. Verification of this concept would have important implications.

Some data (2, 3, 4) have been published on the duration of this phase in normal human subjects, but little data have been presented concerning subjects with heart disease (v.i.) (3, 4, 5). The development of the electrokymograph (6, 7) provides a new and convenient method of measuring the duration of ventricular isometric relaxation (8). This instrument was used to study and compare a series of normal persons and persons with heart disease in order to further evaluate the measurement of this interval.

## MATERIALS AND METHOD

*The Electrocardiograph.* The electrokymograph<sup>5</sup> is an apparatus specifically designed as an attachment for use with the roentgenoscope and electrocardiograph. When these three units are utilized together for the purpose of electrokymography, the basic function of each is as follows: the roentgenoscope provides the means for observing the cardiovascular silhouette of a subject and for positioning the electrokymographic pickup unit over a selected area; the electrokymograph converts the motions and density changes of such selected points to corresponding current variations; and the electrocardiographic galvanometer records these variations on moving bromide paper. The record

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obtained, an electrokymogram (EKY), reflects the movements and density changes of the border of the heart (9). A carotid sphygmogram is routinely<sup>6</sup> recorded simultaneously for timing and orientation purposes.

*Technique.* Electrokymograms were taken as previously described (6, 9). By placing the patient in the left anterior oblique, anterior-posterior and right anterior oblique positions the motions of seven portions of the ventricular silhouette were recorded. Eight to 10 cardiac cycles were recorded in each position with the patient standing and respiration arrested at mid-inspiration or mid-expiration. On some subjects, of both groups, the blood pressure and heart rate were taken immediately before and after obtaining the records to determine whether or not a change in either occurred. No appreciable changes were noted.

*Left Ventricular Electrocardiogram.* The physiological basis of interpreting the electrokymogram has been presented previously (6, 7, 9). The ventricular electrokymograms are found to be surprisingly similar to volumetric curves of the ventricles obtained by direct cardiometer methods in animal experimentation. Though they reflect volumetric changes to a remarkable degree, they also show effects from pendulum movement, rotation and shape changes of the heart. Each cycle (fig. 1) consists of a major descending limb, due essentially to the medial movement of the ventricular border during systole, and an ascending limb associated with lateral movements of the wall in diastole. At the junctions of these limbs are serrations and changes related to other intrinsic events occurring during the cycle. The vertical time lines in the schematic diagram in figure 2 divide the left ventricular electrokymogram into its respective phases. The interval 1-2 is the isometric contraction phase; 2-3 the ejection phase; 3-4 the protodiastolic phase (1); 4-5 the isometric relaxation phase; 5-6 the rapid filling phase; and 6-1 the slowed filling phase.

*Left Ventricular Isometric Relaxation Phase.* This phase is commonly defined as that interval between the closure of the semilunar valve and the opening of the auriculo-ventricular valve. In the normal left ventricular curves of figure 3, this phase is identified by the vertical time lines, 4-5. Point 4 is related to the closure of the aortic valve and point 5 is related to the opening of the mitral valve. The interval between these two points represents the duration of the isometric relaxation phase and provides an easy means of measuring this phase directly on a single curve.

The simultaneously recorded carotid sphygmogram is most convenient to use for orientation purposes and reference to it permits identification of points 4 and 5. Aortic valve closure (point 4, figs. 2 and 3) is identified by the carotid incisura. In most records a clearly defined change of contour occurs on the EKY about 0.04 second prior to the nadir of the carotid incisura and this marks

<sup>6</sup> The phlebogram, electrocardiogram or phonocardiogram may, of course, be utilized depending on the purposes of the investigation.

aortic valve closure. This point on the EKY precedes the corresponding point on the sphygmogram because of the time taken for the transmission of the pulse wave from the aortic valve to the carotid artery (0.02–0.03 sec.) and the lag in the carotid recording system (0.01 sec.). While the opening of the a-v valve (point 5, figs. 2 and 3) is not reflected on the carotid curve itself, approximately 0.08 second after the nadir of the carotid incisura, a sharp change in the EKY occurs which physiologically appears related to a-v valve opening, beginning of rapid filling of the ventricle and outward movement of the ventricular wall. This change point is so consistent as to permit identification of point 5 on most records. In surveying a record, points 4 and 5 are seen to 'straddle' the nadir of the carotid incisura; point 4 commonly lies in the same vertical axis as the shoulder marking the onset of the carotid incisura; point 5 is usually aligned with the peak of the post incisural wave of the carotid (fig. 3).

The point at which the aortic valve closes and the mitral valve opens, with respect to the left ventricular EKY, has been further verified by analysis of varying combinations of simultaneous recordings of the ventricular, auricular and ascending aorta EKY, phonocardiogram and carotid-sphygmogram. These relationships are summarized schematically in figure 2. Figures 3 and 4 are sample records which aided in developing this schematic illustration. Aortic valve closing is identified by the onset of the second heart sound. In figure 3, heart sounds were simultaneously recorded with left ventricular EKY and the carotid sphygmogram. The vertical time line 4 drawn from the onset of the second heart sound is seen to coincide with point 4 on the EKY which is thus identified as aortic valve closure.

The opening time of the mitral valve on the ventricular EKY, vertical line 5, figures 2 and 4, is identified by means of the left atrial EKY. The cycles chosen for comparison are necessarily of the same length. Vertical line 1, figure 2, marks the closure of the mitral valve on the atrial and ventricular electrokymographic curves. The ascending limb of the atrial curve between vertical lines 1 and 5 (point 'v') represents the filling (outward motion) of the left atrium. While the closed mitral valve separates the atrium from the ventricle during this phase, the forceful ventricular contraction which is underway nevertheless produces transmitted effects on the atrial curve. These effects are evidenced by two sets of serrations. The left or first serration is related to the onset of ventricular ejection (x peak). While the second serration at line 4 is related to aortic valve closure. 'V' marks the end of atrial filling and the onset of the descending limb (inward motion) which is related to atrial emptying. This emptying proceeds rapidly up to vertical line 6, slows and at point 'A' atrial contraction begins producing a further sharp descent to line 1 where the mitral valve again closes.

Supporting evidence relative to the opening of mitral valve is shown in figure 5 in a case of mitral stenosis. The sound of the opening snap 'S' is seen to

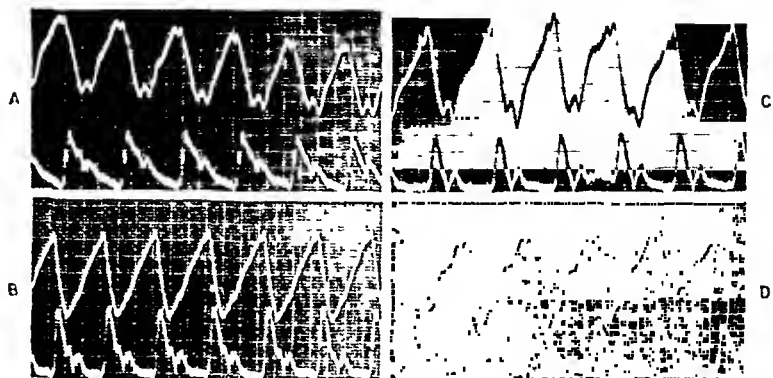


Fig. 1. SAMPLES of the left ventricular electrokymograms from normal persons. Lower curve in each sample is carotid sphygmogram. By utilizing the interpretive method described in the text and illustrated in fig. 2, isometric relaxation and other phases of the ventricular cardiac cycle may be identified.

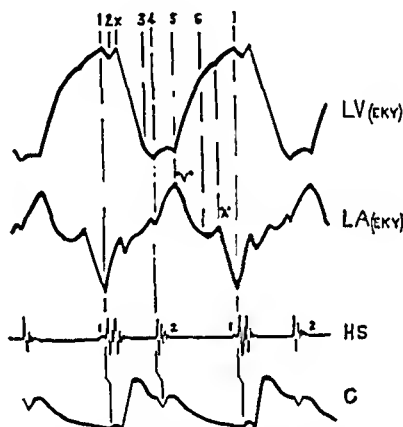


Fig. 2. SCHEMATIC DRAWING of the method of interpreting electrokymograms of the left ventricular border (LV) utilizing the left atrial (LA) EKY, the heart sounds (HS) and the carotid sphygmogram (C). The vertical lines indicate the phases of the cardiac cycle according to Wiggers.

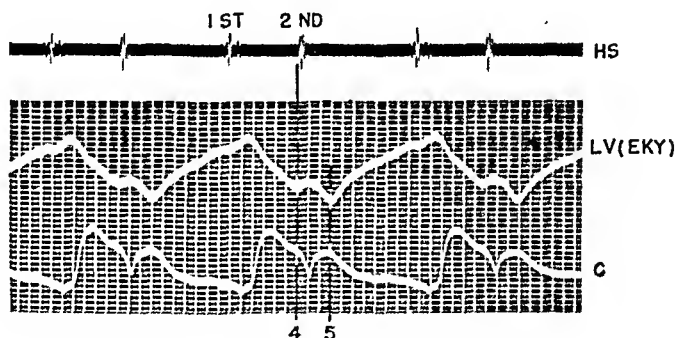


Fig. 3. RECORD OF HEART SOUNDS, left ventricular EKY and carotid sphygmogram of normal subject. Onset of 2nd heart sound coincides with point 4 of left ventricular EKY, identifying closure of semilunar valves and onset of isometric relaxation. Film speed 50 mm/sec.



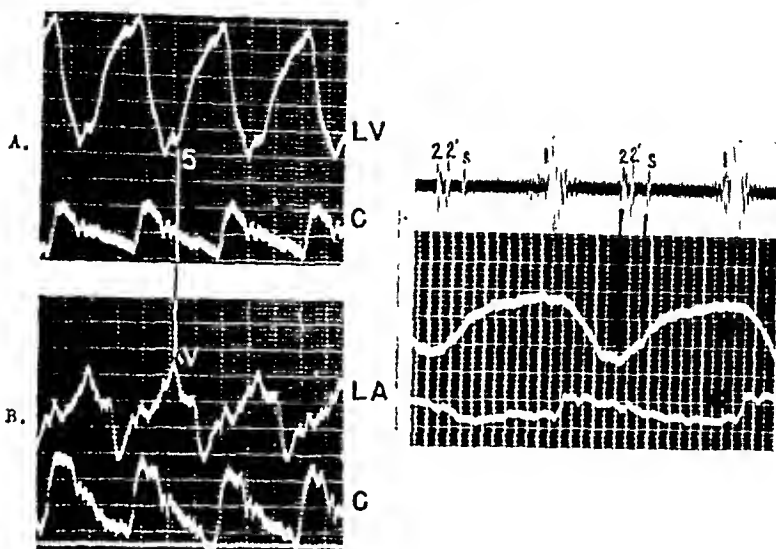


Fig. 4 (left). IDENTIFICATION of opening of mitral valve on left ventricular EKY (LV) by cross correlation with left atrial EKY (LA) on same subject. Carotid sphygmograms (C) of equal cycle length used as time reference curve and records aligned through incisura. Mitral valve opening at points 5 and 'v'.

Fig. 5 (right). LEFT VENTRICULAR EKY (middle curve) and heart sounds of a case of mitral stenosis with an opening snap of mitral valve 'S', showing relationship of the snap 'S' to point 5 on EKY. Film speed 50 mm/sec.

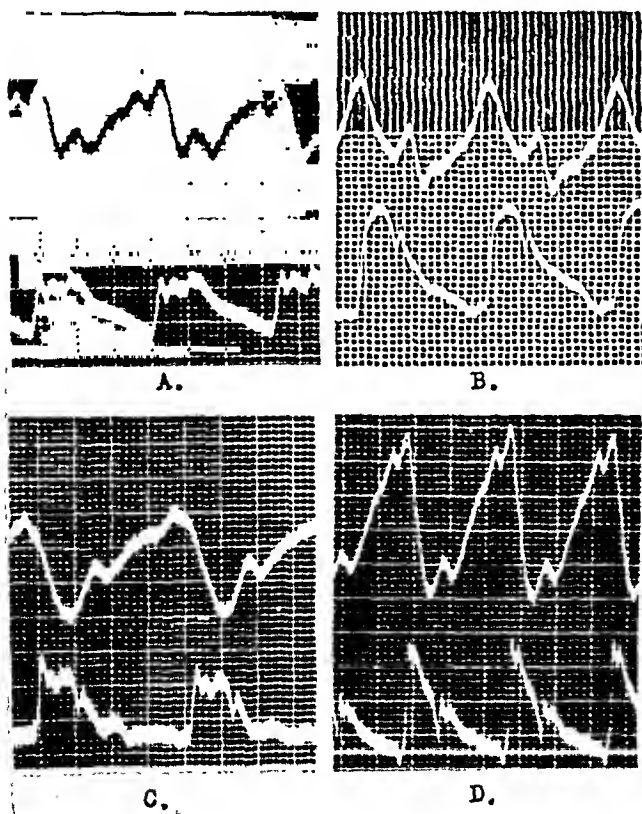


Fig. 6. REPRESENTATIVE RECORDS of cases of heart disease. (A) Hyper-tensive heart disease. Isometric relaxation 0.16 sec. (B) Left bundle-branch block. Isometric relaxation 0.16 sec. (C) Posterior myocardial infarction. Isometric relaxation 0.20 sec. (D) Normal record. Isometric relaxation 0.12 sec.

coincide with the point on the ventricular EKY indicated as the opening of the mitral valve.

The form of the ventricular curve between points 4 and 5 has certain normal variations from that shown in the schematic drawing. Some of these variations are shown in figures 1 and 3. While points 4 and 5 are commonly on the same horizontal level, they may vary upward or downward in their relationship to one another. Occasionally instead of appearing as sharp peaks, they appear as a thickened slur on the main limbs of the curve, figures 1 B and 5

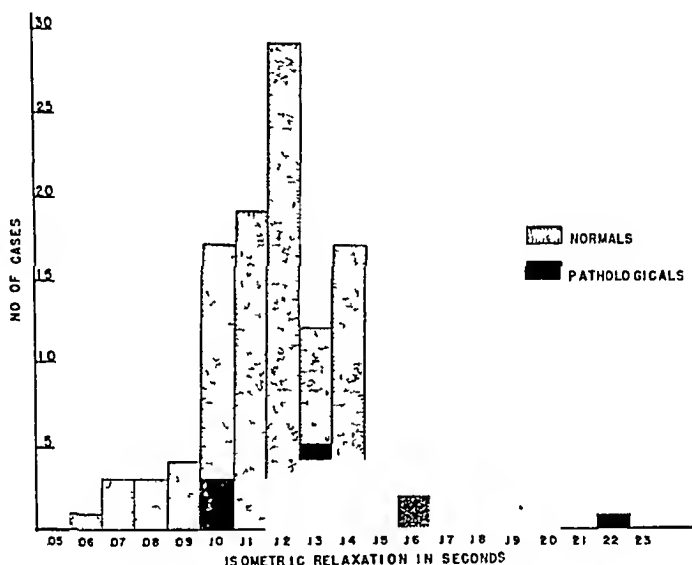


Fig 7

The curve inscribed by ventricular border movement during isometric relaxation is believed due to positional change of the border which occurs with the return of the heart to its resting position. As would be expected, the movement varies from subject to subject and in different parts of the ventricle of a single subject. Physiologically no volumetric changes occur during this period in normal hearts.

## RESULTS

The duration of the isometric relaxation phase could be measured on 108 or 95 per cent of 114 normal subjects, age 17 to 32 years. Approximately 20 cycles per subject were read, thus the over-all study consisted of some 2000 cycles. Only those cycles were measured and recorded in which the phase of isometric relaxation could be easily identified.

Figure 7 and table 1 represent the data of the normal and pathological groups. The stippled columns of figure 7 represent the data from the normal

group and the solid black columns represent the data from the pathological group. The duration of the isometric relaxation phase in the normal group ranged from 0.06 to 0.16 second, the mean value being 0.115 second. The probable error was 0.013 second. It was found that 71 per cent of the cases were within the range of  $0.115 \pm 0.013$  second or 0.10 to 0.13 second. The duration of this phase was found to be independent of age, sex, systolic, diastolic and pulse pressure and cycle length.

TABLE 1. SUMMARY OF RESULTS OF STUDY OF ISOMETRIC RELAXATION IN NORMAL AND PATHOLOGICAL SUBJECTS

	NO. OF SUBJECTS	RANGE	$\pm 1$ P.E.	MEAN
		sec.	sec.	sec.
Normal subjects.....	108	0.06-0.16	0.10-0.13	0.115
Abnormal subjects.....	79	0.10-0.22	0.15-0.18	0.169

TABLE 2. DISTRIBUTION OF DURATION OF ISOMETRIC RELAXATION ACCORDING TO TYPE OF PATHOLOGY

	HYPERTENSIVE HEART DISEASE	MYOCARDIAL INFARCTION			BUNDLE-BRANCH BLOCK		
		Post.	Ant.	Total	Left	Right	Total
0.10		1	1	2	1		1
0.11							
0.12	3				1		1
0.13		3	1	4			
0.14		2	1	3	1		
0.15	2	1	1	2			
0.16	8		2	2	2	1	3
0.17	4	2	3	5	1	2	3
0.18	8	2	1	3	3	2	5
0.19	4	1	1	2	1	2	3
0.20	4	1	2	3	1		1
0.21							
0.22						1	1
Total.....	33	13	13	26	11	8	19
Mean.....	0.1703 sec.	0.1546	0.1631	0.1588	0.1618	0.1850	0.1705

However, in some preliminary studies the heart rate and blood pressure of an individual subject were varied by inhalation of amyl nitrite. In these subjects the duration of isometric relaxation appeared to vary directly with the cycle length, but appeared independent of the blood pressure changes.

The records of 79 subjects with hypertensive heart disease, myocardial infarction and bundle-branch block were studied in a manner similar to the normal. The data obtained are represented by the solid black columns, figure 7. The range of duration was from 0.10 to 0.22 second; the mean value was 0.169 second. The probable error was 0.017 second. Seventy per cent

of the cases were within the range of  $0.169 \pm 0.017$  second or 0.15 to 0.18 second. As indicated in table 2 this increase in the duration of the isometric relaxation phase was common to each of the types of heart disease included in the study. Neither the degree of increase nor the contour of the isometric relaxation complex appeared characteristic for any one of these types of heart disease.

The difference between the mean of the normals (0.115 sec.) and the mean of the abnormals (0.169 sec.) was 0.054 second and by statistical study was found to be significant. The duration of this phase was 0.14 second or less in 98 per cent of the normal readings and 0.15 second or more in 80 per cent of the pathological readings.

In measuring the duration of isometric relaxation on successive cycles from one portion of the ventricle, variations of 0.01 to 0.02 second were found.

TABLE 3. COOPERATIVE TABLE OF METHOD AND RESULTS OF STUDIES OF ISOMETRIC RELAXATION IN NORMAL HUMAN SUBJECTS

AUTHOR	METHOD	NO. IN STUDY	RANGE	PREDOMINANT RANGE	MEAN
			sec.	sec.	sec.
Weitz	Cardiogram	21	0.054-0.156		0.116
Burstein	Phlebogram and sphygmogram	50	0.037-0.130	0.06-0.09	0.076
Bohning & Plaut	Phlebogram and sphygmogram	15	0.040-0.200	0.08-0.14	
Boone, <i>et al.</i>	EKY	108	0.06-0.16	0.10-0.13	0.115

<sup>1</sup> Utilizing  $\pm 1$  P.E.

Comparison of one portion of the ventricle with another showed an occasional variation of as much as 0.03 second. Since the average of several cycles from different areas of the ventricle were taken, such variations were not sufficient to throw a normal subject into the pathological group or vice versa. These differences in the duration of this phase may be attributed to physiological changes occurring from cycle to cycle and to an error in reading of 0.01 second.

## DISCUSSION

Although some workers have suggested the possible significance of this phase of the cardiac cycle in man, relatively little work has been reported (1-4). This fact may have been due to the limitations of the methods available. The studies of Weitz *et al.* are summarized in table 3.

Many factors limit the use of the apex cardiogram, as utilized by Weitz, as a routine method of studying the phases of the cardiac cycle. Among these are the technical difficulties of taking and interpreting a record, the variability of patterns and the difficulty of reproducing results.

The method of study employed by Burstein, and by Bohning and Plaut, consisted of the cross correlation of the sphygmogram and the phlebogram. The necessity of employing two recordings in order to obtain a measurement is in itself an undesirable feature. Asynchronism (10) between the left and the right side of the heart is not accounted for in this method. An additional difficulty in its routine use is the difficulty of obtaining readable and sharply defined phlebograms.

Past studies of subjects with heart disease have been done mainly by Weitz (3), Margolies and Wolferth (5) and Bohning and Plaut (4). These workers for the most part have concentrated their efforts in a study of valvular disease. Thus, it is difficult to make a comparison of our results with the results of other reports, except for Weitz who studied eight cases of hypertension with which we can make a comparison. The range of isometric relaxation in these eight cases was 0.06 to 0.175 second. Our range for 33 hypertensive cases was from 0.12 to 0.20 second.

It is felt that the method presented in this study answers many of the problems of past studies. The method is easily performed with no discomfort to the subject, with a high percentage of readable records. The interval is easily identified, measured and the results may be reproduced.

It is of interest to conjecture as to the possible cause or causes of the increased duration of isometric relaxation in the cases with heart disease. Four possible factors have been suggested which may individually or in combination effect the duration of the phase of isometric relaxation (1). These factors are: the inherent rate of muscular relaxation, the intraventricular pressure at the onset of isometric relaxation, the intra-atrial pressure at the end of isometric relaxation and, finally, the time interval by which the preceding protodiastolic phase is abridged may be added to the phase of isometric relaxation.

In hypertension it may be that two factors are involved in the prolongation of isometric relaxation. 1) The increase of the intra-ventricular pressure at the end of systole results in a greater differential pressure between the ventricle and the auricle (as compared with the normal). This, in turn, increases the interval of time required for the intra-ventricular pressure to fall below the intra-atrial pressure which results in increasing the duration of isometric relaxation. 2) Later as the hypertrophy of the ventricular musculature progresses and its nutrition becomes impaired, the inherent rate of muscular relaxation may be longer.

With the development of congestive failure there is a decrease in the intra-ventricular pressure at the end of systole as compared to the compensated hypertensive state. Further, the intra-atrial pressure existing at the end of ventricular systole is elevated as compared to the compensated state. The

increase in intra-atrial pressure and the decrease in the intra-ventricular pressure results in a decrease in the differential pressure, as compared with the compensated hypertensive state, with an accompanying decrease in the time necessary for the intra-ventricular pressure to fall below the intra-atrial pressure. Therefore, it seems possible that in the decompensated hypertensive subject the duration of isometric relaxation could be within normal limits. Two of the three cases of hypertensive heart disease with values of 0.12 second or isometric relaxation were in congestive failure. The duration of isometric relaxation in these subjects was not known previous to failure, nor was a follow-up possible.

In the cases of bundle-branch block and myocardial infarction, it seems probable that the factor mainly involved in increasing isometric relaxation is associated with metabolic and structural changes within the heart muscle resulting in an increase in time required for the process of relaxation.

It is also of interest to note that during the phase of isometric relaxation there is a large coronary blood volume flow (11). A prolonged isometric relaxation phase might then be a compensatory measure to maintain adequate coronary blood volume flow in the case of coronary insufficiency or to increase coronary blood volume flow in the case of hypertrophy of the myocardium.

These facts and conjectures suggest the need for further study of the physiological factors concerned in the duration of this phase of the cardiac cycle.

#### CONCLUSIONS

The electrokymograph offers an easily applied method of studying the phase of isometric relaxation. The data presented indicate that the duration of the isometric relaxation phase of the cardiac cycle as measured from the electrokymogram has a well defined range in normal human subjects. In a group of subjects with heart disease, the range of isometric relaxation was significantly different from that found in the normal.

Doctor J. L. Lewis, Jr., Baltimore Marine Hospital, kindly supplied some of the records.

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## *Effect of Altered Breakfast Habits on Physiologic Response<sup>1</sup>*

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THE PROBLEM of eating habits has demanded considerable attention and investigation both from the standpoint of health and industrial efficiency. Many ideas based on purely theoretical grounds have been suggested as rules to follow in the matter of eating habits. For example, the athlete has been cautioned against eating heavy meals and certain types of food during competition days. It is generally accepted that heavy work should not be attempted with the stomach full of food, and that water should not be ingested during the intermission between strenuous bouts of exercise, except in small quantities. The data which seem to support many of these ideas appear to be observations and experiences obtained by those engaged in strenuous work.

Meal-spacing is usually arranged from the standpoint of convenience rather than as an attempt to meet the optimum physiologic demands of the body for energy. Haggard and Greenburg (1-4) pursued the idea that the maintenance of a high blood sugar level was conducive to high work efficiency. If true, it seemed reasonable to assume that if the characteristic drop in blood sugar which occurs between meals could be avoided by between-meal feeding, work efficiency would be improved. Haggard and Greenburg (2) also reported that the consumption of a meal increased muscular efficiency significantly, but a repetition of this work by Haldi *et al.* (5) failed to confirm this effect. In a subsequent experiment, Haldi and Wynn (6) failed to find any beneficial effects in work output resulting from mid-morning and mid-afternoon feeding of factory workers regardless of the amount or kind of the food eaten at these times. When rest periods were substituted for food, the results were also negative.

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Supercharging the body with food seems to fall into the same category as supercharging it with vitamins, in that nothing is gained as far as capacity to do work is concerned. However, in considering meal-spacing, other factors such as the distraction of hunger, boredom with the task at hand, as well as available fuel for work, must be taken into account. This is suggested by the report of Mann (7) which states that the greatest percentage of industrial accidents occurs between 11 A.M. and 12 noon.

Breakfast habits deserve special consideration from the standpoint of irregularity and the omission of the morning meal. This is especially true because irregularity of breakfast habits, in many instances, is caused by a poorly arranged morning schedule. Where the breakfast is omitted or eaten under the pressure of time, inefficiency may result from an accentuation of any tendency toward nervous reaction to the forenoon tasks.

In the present study an attempt has been made to show the effects of altered breakfast habits on *a*) maximum work output, *b*) simple and choice reaction time and *c*) neuromuscular tremor.

#### METHOD

*Maximum Work Output.* In measuring maximum work output one must recognize the fact that the results represent the amount of work a subject will do rather than the amount he is capable of doing. This situation calls for careful experimental management and planning so as to avoid variable motivation during the work period. Another problem which must be considered in the measurement of maximum work output is that as a result of each preceding bout of exercise the subjects improve, and continue to do so over a rather long period of time. This improvement phenomenon has been shown in this laboratory by Wilson *et al.* (8) and by others, among them Karpovich and Pestrecov (9). This leaves two alternatives in studying the effect of any variable on maximum work output. The first is, subjects may be trained by performing daily bouts of exercise until they cease to improve, that is reach a plateau, and the second alternative is to allow the element of improvement to operate but recognize it as an influencing factor. Suppose, for example, that during a 9-week period subjects work for 3 weeks under normal conditions, 3 weeks under altered conditions, followed by a 3-week control period. If the maximum work output gradually increases during the first control period, decreases or remains unchanged during the period of altered conditions but again improves during the second control period, it is quite safe to conclude that the experimental conditions imposed caused a decrease in maximum work output. This latter procedure was followed in the experiment herein reported.

In this, as in any experiment involving the measurement of maximum work output, the first problem is the selection of an amount of work which the subjects can perform well and at the same time which will differentiate between small changes in work capacity. Experience has shown that to measure small changes (or large ones) in maximum work output an exercise must be adopted which provides sharp end points if quantitative data are to be calculated. The

bicycle ergometer (as described by Tuttle and Wendler, 10) is satisfactory for this type of measurement of maximum work output.

The work consisted of riding the bicycle at maximum effort for one minute. A work record is shown in figure 1. One minute of work was selected since experience showed that by extending the work some subjects showed exhaustive reactions such as nausea, vomiting, dizziness and muscle soreness. These symptoms had to be avoided, because the exercise had to be repeated at regular intervals and the subjects resented these reactions. By limiting the work period the subjects are more apt to exert greater initial effort because of the absence of psychologic reactions to the effects of exhaustive exercise. It was proven in this laboratory that an extension of the work period did not markedly improve the test validity since the maximum work output for one minute correlated 0.94 with the maximum work output for two minutes. The

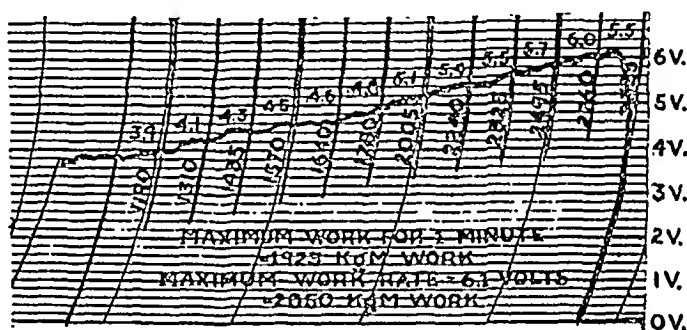


Fig. 1. RECORD OF MAXIMUM WORK OUTPUT for one minute recorded in volts. The mean work equivalent to the voltage generated for each 5-second interval is written on the record.

amount of work done in the one-minute period was found by laying off 12 five-second intervals on the work record as shown in figure 1. The mean voltage for each five-second interval was calculated and written on the work record. With the use of a calibration table constructed by Tuttle and Wendler (10), the work equivalent to the voltage reading was recorded for each five-second interval. The average maximum work output for the 12 five-second intervals is the work performed in one minute.

**Reaction Time.** Since it is well established that reaction time is sensitive to changes in physiologic condition, this test was adopted as a possible means of detecting changes brought about by altered breakfast habits. In this experiment reaction time is defined as the interval elapsing between the appearance of a light stimulus and the response to it made by pressing an acro-snap switch with the index finger. The reaction time was recorded in milliseconds by means of a Dunlap chronoscope, specially arranged for this purpose. Electric circuits were arranged so that simultaneously with the flash of the stimulus light the chronoscope hand started. The chronoscope hand stopped when the subject closed the switch with the index finger.

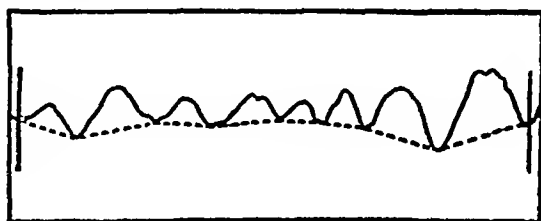
So as to provide for the measurement of choice reaction time the stimulus light was placed as number 1 in a bank of five. The lamp bank was so arranged that light 1 could be lit without starting the chronoscope hand. This arrangement provided means whereby practice trials and a variety of patterns could be given without resetting the chronoscope after each trial. Both simple and choice reaction times were employed in this experiment. In case of the former the subject was shown light 1 only and she responded to it as fast as possible. The choice reaction time pattern consisted of flashing any or all the lights in a promiscuous fashion, the subject being instructed to respond to light 1 only.

The subjects were alone in a room equipped with a dim red light. The room was some distance from the chronoscope. Before each experiment the subject was allowed time for dark adaptation. Not only was each subject given several practice periods before experimentation started but also she was allowed several practice trials before each set of measurements was taken. Each subject performed 50 trials of simple and 30 trials of choice reaction time. Since no rest period was allowed in the reaction time series the choice reaction time responses were limited to 30.

*Tremor.* The presence of tremor in man is recognized as a normal physiologic phenomenon. Wolfenden and Williams (11) were the first to make systematic records of tremor. Aside from pathologic implications, the tremor studies reported have dealt with its character, factors influencing it, origin, rate and amplitude, and classification. Eshner (12) concluded from his studies that tremor was characterized by irregularity and that frequency and extent were inversely related. Binet (13) proposed what he called 'The Law of Tremor' in an attempt to classify factors influencing it. The origin of tremor has been investigated by Jasper and Andrews (14), Travis and Hunter (15), Fulton, Liddell and Rioch (16), Aring and Fulton (17) and Sollenburger (18). The consensus seems to be that tremor is a result of postural contraction inherent in the simplest reflex arc. It is independent of the higher centers for its origin although it is modified by the activity of higher centers. The rate at which tremor occurs has been studied by Herren (19) and Bousfield (20) who conclude that for the upper extremity the rate varies from 5 to 12 per second. Clinically Bucy (21) divides tremor into two main groups which he designates as tremor at rest, that is, those which occur in parts which are supported but which are not at the time involved by voluntary muscular contractions, and intention tremor, also known as action tremor, which occurs in the part when its musculature is being voluntarily contracted. Static tremor is a manifestation of intention tremor and is present when an extremity is being held still unsupported except by voluntary resistance against the force of gravity. The investigation herein reported is designed to show the effect of alteration of breakfast habits on the nature of static tremor.

Static tremor was recorded from the outstretched right arm, unsupported except by voluntary resistance against the force of gravity both before and after a one-minute bout of strenuous exercise on a bicycle ergometer. The index finger of the unsupported arm barely touched an electric generator. The generator consisted of a permanent magnet loud speaker, with a button attached to the armature, which was in contact with the finger. The generator was supported on a ring stand adjusted to the proper height. The tremor of the outstretched arm activated the speaker by generating voltage in the armature. In order to amplify the voltage generated in the armature of the speaker, advantage was taken of one channel of an Offner E. E. G. The voltage was amplified sufficiently to activate a crytograph recorder. Before

Fig. 2. NEUROMUSCULAR TREMOR RECORD. The score is found by determining the area under the curves occurring during the period of one second as set off by the vertical lines.



each experiment the recorder was standardized so that a test signal of 3000 v. caused a pen swing of 14 mm. A tremor record is shown in figure 2. The recording paper was pulled past the pen at a rate of 10 cm/second. The tremor score was determined as follows. A strip of tremor record 10 cm. long was measured off. A line was drawn from trough to trough of each consecutive tremor contained in the 10-cm. (1 sec.) strip. The total area of the tremor for 1 second was used as the score. This was found by tracing the boundary of the tremor with a planimeter. The scores take into account both amplitude and rate. By multiplying the planimeter readings by 16.77 the score is expressed in sq. cm.

*Subjects.* Six healthy, normal women ranging in age from 22 to 27 years were used in this study. The subjects were housed as a unit in an attempt to minimize temptation during periods of abstinence from breakfast. To our knowledge no subject broke the dietary regime during any of the experiments. The subjects were fed the specified breakfasts by trays prepared in the diet kitchen of the University Hospitals under the supervision of the Department of Nutrition. All subjects were graduate students and were relatively consistent in eating, sleeping and exercise habits.

The subjects pursued their regular schedule in all respects except that their breakfast habits were controlled, and they spent the hour immediately preceding luncheon (11:00 A.M. to 12 noon) in the laboratory performing the experimental routine.

*Breakfast Classification.* Four breakfast classifications were used to vary

experimental conditions, viz., a heavy breakfast, a light breakfast, coffee only, and omission of breakfast. The heavy breakfast consisted of fruit, cereal and cream, 1 egg, bacon (1 slice), toast (2 slices), and jam, milk, and coffee if desired. The caloric value was approximately 800. The light breakfast consisted of fruit, one slice toast, butter, milk, and coffee if desired, and had a caloric value of approximately 400. Omission of breakfast was defined as abstinence from food intake between 6:00 P.M. (dinner) and 12 noon (lunch) the following day. The 'coffee' breakfast was regulated the same as omission of breakfast except that one cup of coffee with one ounce of cream and no sugar was taken in the morning at the breakfast hour.

A series of three experiments were performed to show any effects that altered breakfast habits might have on the physiologic responses described.

**EXPERIMENT 1.** This experiment was undertaken as an exploratory study to determine if it were possible to demonstrate differences in physiologic responses to heavy breakfasts and no breakfast. The experiment consisted of three consecutive 3-week periods. During the first period all 6 subjects ate the heavy breakfast; during the second period 3 subjects ate the heavy breakfast and 3 subjects omitted breakfast; during the third the procedure for the second period was rotated. Thus, 'no breakfast' status could be compared with 'heavy breakfast' status both for individual subjects and for groups of subjects. Behavior changes, which were extraneous to the breakfast variable, also could be detected. Data were collected once each week for three performance tests: work output, reaction time and tremor pattern. The testing period for all three experiments was limited to the hour preceding the noon lunch and was kept constant as to time of day and day of the week for a given subject.

The results of this experiment showed sufficient differences in subject behavior to heavy breakfasts and no breakfast to warrant a continuation of the study. Although there was no change in work output, reaction time responses showed a group tendency toward an increase when breakfast was omitted and the tremor magnitude was significantly increased in every case when no breakfast was eaten.

**EXPERIMENT 2.** This experiment, which is actually a repetition of a part of *Experiment 1*, was designed to meet two specific purposes: 1) to determine whether the tendencies and positive changes in *Experiment 1* could be repeated and 2) to determine whether all differences would be significant if data were collected more frequently. The experiment consisted of two consecutive 3-week periods. During the first period all subjects ate the heavy breakfast and during the second all subjects omitted breakfast. Data were collected between 11:00 A.M. and 12 noon, twice each week from each subject for the three tests. This procedure insured ample data for analysis of each test investigated, that is, work output, reaction time and tremor pattern.

1) *Maximum work output.* The summary of the 6 records per subject of work output for each period and the analysis thereof are shown in table 1. Five of the 6 subjects showed a highly significant decrease in maximum work output when breakfast was omitted. The scores of the other subject remained practically unchanged.

2) *Reaction time.* The summary of reaction time data for *Experiment 2* (both simple and choice responses), collected bi-weekly for each of the 6 subjects, is tabulated by periods in table 2. Reaction time for each subject increased during the no-breakfast period; 5 of the 6 subjects showed a significant change in the simple responses but only 3 subjects showed a true increase in choice response time.

TABLE 1. EFFECT OF ALTERED BREAKFAST HABITS ON MAXIMUM WORK OUTPUT OF 6 SUBJECTS DURING TWO PERIODS OF THREE WEEKS DURATION EACH. EXPERIMENT 2, BREAKFAST  
vs. NO BREAKFAST

	SUBJECTS						Av.
	1	2	3	4	5	6	
<i>Period 1</i>							
Heavy breakfast							
M(Kg.M.).....	1869	2053	2300	1641	1916	2215	1999
S.D.....	50.0	36.1	41.9	54.5	51.9	42.0	17.6
<i>Period 2</i>							
No breakfast							
M(Kg.M.).....	1767	1917	2017	1511	1725	2194	1855
S.D.....	28.9	65.6	49.5	61.9	96.9	67.6	28.8
<i>t</i> (1 vs. 2).....	3.81	3.73	9.10	3.30	3.56	0.54	8.78
Signif. level.....	1%	1%	0.1%	1%	1%	60%	0.1%

3) *Tremor.* As in *Experiment 1* each of the 6 subjects demonstrated a highly significant increase in the magnitude of tremor pattern before exercise when breakfast was omitted. After exercise only 5 subjects demonstrated this significant change. The summary and analysis of these data are given in table 3.

EXPERIMENT 3. This experiment consisted of three consecutive 3-week periods. During the first period all subjects ate the heavy breakfast, during the second all subjects consumed coffee only for breakfast and during the third all subjects ate the light breakfast. Data were collected twice a week, as in *Experiment 2*, for work output, choice reaction time and tremor pattern.

1) *Maximum work output.* The summary of data given in table 4 is compiled from four records per subject during period 1, five per subject during period 2 and four per subject during period 3. Five work records were lost during this 9-week experiment because of temporary mechanical failure of the

bicycle ergometer. The group means for each test of work output are plotted in chronological order in figure 3B.

A comparison of the means (by subjects) for the heavy breakfast period with those for the coffee period (table 4) shows that 5 of the 6 subjects did less work during the coffee period. Only 3 of these differences were statistically

TABLE 2. EFFECT OF ALTERED BREAKFAST HABITS ON SIMPLE AND CHOICE REACTION TIME OF 6 SUBJECTS DURING TWO PERIODS OF THREE WEEKS DURATION EACH. EXPERIMENT 2, BREAKFAST VS. NO BREAKFAST

	SUBJECTS						
	1	2	3	4	5	6	Av.
<i>Simple Reaction Time</i>							
<i>Period 1</i>							
Heavy breakfast							
M(sec.).....	0.299	0.302	0.249	0.246	0.238	0.227	0.260
S.D.....	0.016	0.010	0.011	0.016	0.022	0.004	0.009
<i>Period 2</i>							
No breakfast							
M(sec.).....	0.315	0.325	0.264	0.268	0.277	0.237	0.281
S.D.....	0.013	0.014	0.006	0.009	0.021	0.008	0.005
<i>t</i> (1 vs. 2).....	1.78	2.63	3.00	2.75	2.79	2.50	4.00
Signif. level.....	20%	5%	2%	5%	2%	5%	1%
<i>Choice Reaction Time</i>							
<i>Period 1</i>							
Heavy breakfast							
M(sec.).....	0.335	0.388	0.316	0.280	0.272	0.308	0.317
S.D.....	0.012	0.030	0.005	0.009	0.008	0.027	0.005
<i>Period 2</i>							
No breakfast							
M(sec.).....	0.366	0.391	0.340	0.301	0.284	0.330	0.335
S.D.....	0.010	0.010	0.008	0.009	0.025	0.027	0.009
<i>t</i> (1 vs. 2).....	4.43	0.21	6.00	3.50	1.00	1.29	3.60
Signif. level.....	1%	90%	0.1%	1%	40%	30%	1%

significant. If coffee represented an adequate breakfast each subject would be expected to demonstrate a gradual increase in work output proceeding from the level established at the end of period 1 (fig. 3B). Instead, there was a precipitous drop in work efficiency at the beginning of the coffee period. Although there was subsequent improvement, the level of efficiency at the end of the coffee period never reached that which maintained at the end of the heavy breakfast period.

When the individual means for period 3 (table 4, light breakfast) are compared with the respective means for periods 1 and 2, it will be noted that, without exception, the mean outputs for period 3 are greater than those for either of the preceding periods, i.e., each subject regained or surpassed her original work status while eating a light breakfast. These progressive changes

TABLE 3. EFFECT OF ALTERED BREAKFAST HABITS ON MAGNITUDE OF NEUROMUSCULAR TREMOR OF 6 SUBJECTS DURING TWO PERIODS OF THREE WEEKS DURATION EACH, BOTH BEFORE AND AFTER ONE MINUTE OF MAXIMUM WORK. EXPERIMENT 2, BREAKFAST vs. NO BREAKFAST

	SUBJECTS					
	1	2	3	4	5	6
<i>Before Exercise</i>						
<i>Period 1</i>						
Heavy breakfast						
M(sq. cm.).....	1.6	1.5	1.4	1.3	1.6	1.7
S.D.....	0.38	0.36	0.39	0.34	0.24	0.36
<i>Period 2</i>						
No breakfast						
M(sq. cm.).....	2.5	2.2	2.3	2.1	2.6	2.4
S.D.....	0.29	0.29	0.41	0.64	0.29	0.34
<i>t</i> .....	4.21	3.38	3.56	2.47	5.96	3.17
Signif. level.....	1%	1%	1%	5%	0.1%	1%
<i>After Exercise</i>						
<i>Period 1</i>						
Heavy breakfast						
M(sq. cm.).....	3.4	2.3	2.6	2.3	2.7	3.0
S.D.....	0.71	0.43	0.68	0.53	0.48	0.83
<i>Period 2</i>						
No breakfast						
M(sq. cm.).....	3.7	3.4	3.4	2.9	3.4	4.0
S.D.....	0.41	0.39	0.39	0.43	0.48	0.83
<i>t</i> .....	0.82	4.23	2.28	1.97	2.30	1.90
Signif. level.....	50%	1%	5%	10%	5%	10%

through the three periods are more strikingly demonstrated when consecutive group means are plotted (fig. 3B). Statistical comparisons of the individual means for periods 2 and 3 show that 5 of the 6 subjects improved significantly when changed from coffee to a light breakfast. Individual work output differences between heavy and light breakfasts could not be compared statistically because 1) there was no way of establishing the residual effects of the coffee



period and 2) the expected normal increase during the last three of the nine weeks of experimentation on the bicycle ergometer was not established for these subjects.

2) *Reaction time.* Choice reaction scores for each subject for the six records taken bi-weekly during each of the three experimental periods are summarized in table 5. Each record score represents an average of 50 responses all of them being given without interruption during the same test. In an attempt to accentuate any difference which might exist in choice reaction times

TABLE 4. COMPARISON OF MAXIMUM WORK OUTPUT DURING 3-WEEK PERIODS OF HEAVY BREAKFAST, COFFEE ONLY, AND LIGHT BREAKFAST. EXPERIMENT 3

	SUBJECTS						
	1	2	3	4	5	6	Av.
<i>Period 1</i>							
Heavy breakfast							
M(Kg.M.).....	1850	2102	1986	1529	1876	2275	1937
S.D.....	35.7	13.9	53.1	79.2	47.8	21.9	16.7
<i>Period 2</i>							
Coffee only							
M(Kg.M.).....	1831	1952	1924	1604	1728	2236	1877
S.D.....	30.0	89.5	67.9	113.5	39.6	26.9	35.1
<i>Period 3</i>							
Light breakfast							
M(Kg.M.).....	1878	2161	2283	1612	1945	2339	2036
S.D.....	27.3	35.1	68.4	52.3	44.0	70.6	15.5
<i>t</i> (1 vs. 2).....	0.77	2.93	1.16	0.99	4.47	2.06	2.76
Signif. level.....	50%	5%	30%	40%	1%	10%	5%
<i>t</i> (2 vs. 3).....	2.15	3.88	6.08	0.12	6.85	2.65	7.43
Signif. level.....	10%	1%	0.1%	—	0.1%	5%	0.1%

the number of responses was increased from 30 to 50. The choice reaction time score tends to improve with repetition as is demonstrated by the group scores plotted for periods 1 and 3 in figure 3C. However, during period 2, when breakfast consisted of coffee, *subjects 5 and 6* only (table 5) showed this characteristic improvement; all others tended to decrease in efficiency. A comparison of the group means for periods 1 and 2 gives a *t* of 0.33 which is an indication of no change in choice reaction time status for the entire group (table 5).

During period 3, when subjects were eating a light breakfast, there was an abrupt improvement of choice reaction time scores over both periods 1 and 2. This was evidenced by the first record (fig. 3C, period 3). When individual

means for period 3 (light breakfast) are compared with the respective means for period 2 (coffee) all subjects show a significant improvement in reaction time scores. Simple reaction time was not measured during this experiment.

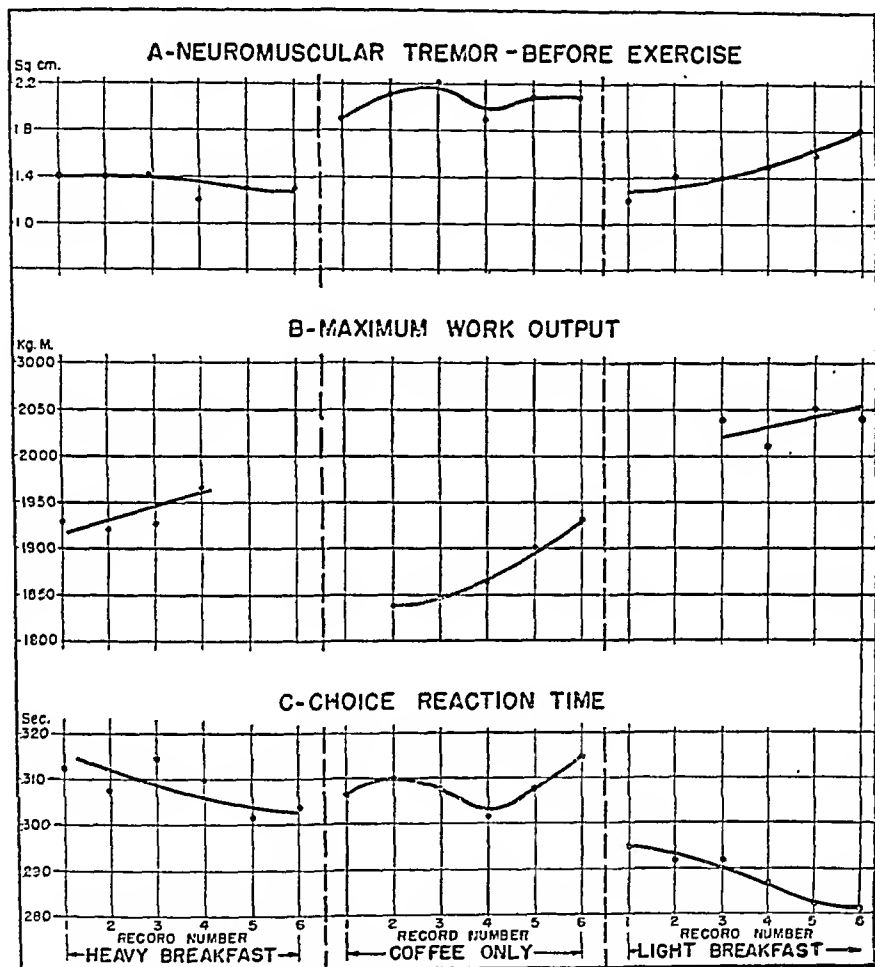


Fig. 3. GRAPHIC REPRESENTATION of three measures of physiologic response, as indicated, to altered breakfast habits during three 3-week periods of experimentation. The scores plotted are means derived from responses of 6 subjects.

3) *Tremor*. Since tremor pattern is not affected by learning or repetition no progressive decrease in tremor magnitude is expected as the experiment progresses. A summary of the data for the three periods (heavy breakfast, coffee, and light breakfast) relative to the magnitude of the tremor pattern, taken both before and after strenuous exercise, is given in table 6. A graph of the group means for consecutive records taken before exercise during the three

3-week periods is presented in figure 3A. After exercise data are omitted from the graph since they show the same trend.

Each subject showed a significant increase in tremor magnitude when coffee was substituted for the heavy breakfast for records taken both before and after exercise. A comparison of period 2 (coffee) with period 3 (light breakfast) shows a direct reversal, i.e., subjects tend to return to their heavy-breakfast tremor magnitude status. The latter changes are highly significant for 5 subjects both before and after exercise. The subjects show a tendency for an increase in tremor magnitude during the last week and one half of the experi-

TABLE 5. COMPARISON OF CHOICE REACTION TIME OF 6 SUBJECTS DURING 3-WEEK PERIODS OF HEAVY BREAKFAST, COFFEE ONLY, AND LIGHT BREAKFAST. EXPERIMENT 3

	SUBJECTS						Av.
	1	2	3	4	5	6	
<i>Period 1</i>							
Heavy breakfast							
M(sec.).....	0.339	0.365	0.290	0.283	0.262	0.313	0.309
S.D.....	0.015	0.007	0.018	0.016	0.007	0.008	0.005
<i>Period 2</i>							
Coffee only							
M(sec.).....	0.355	0.366	0.295	0.289	0.253	0.292	0.308
S.D.....	0.018	0.014	0.009	0.007	0.004	0.021	0.004
<i>Period 3</i>							
Light breakfast.....							
M(sec.).....	0.334	0.340	0.273	0.268	0.246	0.268	0.288
S.D.....	0.009	0.017	0.011	0.006	0.005	0.016	0.005
<i>t</i> (1 vs. 2).....	1.45	0.14	0.56	0.75	3.00	2.10	0.33
Signif. level.....	20%	90%	60%	50%	2%	10%	80%
<i>t</i> (2 vs. 3).....	2.33	2.60	3.67	5.25	3.50	2.00	6.67
Signif. level.....	5%	5%	1%	0.1%	1%	10%	0.1%

ment (fig. 3A). This increase may be the result of final examinations, graduate orals, and similar nervous strain encountered by students at the end of the school year.

#### DISCUSSION

We have every reason to believe that all subjects followed the prescribed breakfast menus explicitly. In spite of this fact there are numerous individual variations from the general patterns established by the group. These individual differences are no doubt basic, especially where the nervous system is involved. During an experiment extending over a rather long period of time,

TABLE 6. COMPARISON OF TREMOR MAGNITUDE IN 6 SUBJECTS DURING 3-WEEK PERIODS OF HEAVY BREAKFAST, COFFEE ONLY, AND LIGHT BREAKFAST. EXPERIMENT 3

	SUBJECTS						
	1	2	3	4	5	6	Av.
<i>Before Exercise</i>							
<i>Period 1</i>							
Heavy breakfast							
M(sq. cm.).....	1.4	1.2	1.6	1.2	1.2	1.4	1.3
S.D.....	0.26	0.31	0.28	0.23	0.15	0.38	0.08
<i>Period 2</i>							
Coffee only							
M(sq. cm.).....	2.1	2.1	2.1	1.8	1.8	2.5	2.1
S.D.....	0.29	0.73	0.26	0.41	0.48	0.23	0.12
<i>Period 3</i>							
Light breakfast							
M(sq. cm.).....	1.5	1.4	1.6	1.4	1.6	1.4	1.5
S.D.....	0.26	0.12	0.31	0.26	0.28	0.23	0.19
<i>t</i> (1 vs. 2).....	4.02	2.54	3.07	2.86	2.67	5.53	12.31
Signif. level.....	1%	5%	2%	2%	5%	0.1%	0.1%
<i>t</i> (2 vs. 3).....	3.45	2.11	2.76	1.84	0.80	7.59	6.00
Signif. level.....	1%	10%	5%	10%	50%	0.1%	0.1%
<i>After Exercise</i>							
<i>Period 1</i>							
Heavy breakfast							
M(sq. cm.).....	2.4	2.0	2.4	1.7	2.1	3.6	2.4
S.D.....	0.41	0.24	0.14	0.15	0.31	0.79	0.14
<i>Period 2</i>							
Coffee only							
M(sq. cm.).....	4.3	3.2	3.5	3.0	3.4	4.7	3.7
S.D.....	0.86	0.53	0.58	1.04	0.76	1.04	0.49
<i>Period 3</i>							
Light breakfast							
M(sq. cm.).....	2.8	2.4	2.5	2.3	2.5	2.7	2.5
S.D.....	0.39	0.24	0.46	0.33	0.48	0.56	0.26
<i>t</i> (1 vs. 2).....	4.46	4.49	3.78	2.77	3.54	1.88	5.70
Signif. level.....	1%	1%	1%	2%	1%	10%	0.1%
<i>t</i> (2 vs. 3).....	3.55	3.00	3.02	1.43	2.24	3.78	4.84
Signif. level.....	1%	2%	2%	20%	5%	1%	0.1%

there are environmental situations arising which cannot be controlled. For example, during the examination periods, there was an alteration in tremor and reaction time among the subjects, the extent depending on their basic responses to such situations.

In experiments where women are used as subjects, menstruation sometimes causes a variability of reactions, the extent depending on the individual involved. In some cases, work output was noticeably affected.

In evaluating data relative to measures such as maximum work output and reaction time, it must be recognized that there is an improvement in performance caused by repetition at regular intervals. This improvement continues for a relatively long period of time and becomes progressively less until a plateau is reached. In drawing conclusions, this fact must be taken into account. For example, in *Experiment 3*, the group averages for reaction time were the same during the heavy breakfast period and the coffee period. If coffee had represented an adequate breakfast one has a right to expect that there would have been a progressive decrease in choice reaction time scores.

#### SUMMARY

Data collected twice each week, between 11:00 A.M. and 12 noon, relative to the effect of altered breakfast habits on physiologic response justify the following conclusions.

1. The omission of breakfast caused a decrease in maximum work output, an increase both in simple and choice reaction time, and an increase in tremor magnitude.

2. When coffee alone is substituted for a heavy breakfast there is a decrease in the level of performance in maximum work output, and choice reaction time; there is an increase in tremor magnitude.

3. When a light breakfast is substituted for coffee alone the level of performance of maximum work output and choice reaction time improves significantly; there is a decrease in tremor magnitude.

4. There are considerable individual differences in response to altered breakfast habits.

5. Because the breakfast period of coffee only occurred between heavy breakfast and the light breakfast periods a direct comparison of the physiologic responses during the light and heavy breakfast periods could not be made.

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# *Reproducibility of Values for Oxygen Saturation of Arterial Blood, and Magnitude of Venous-Arterial Shunts in Patients with Congenital Cardiac Malformations*

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IN OUR LABORATORIES, the decrease in oxygen saturation of arterial blood with exercise has been considered a good index of the inadequacy of pulmonary flow in patients with congenital cardiac defects of the cyanotic type (1, 2). It seemed of importance, therefore, to determine whether or not the results of such studies of oxygen saturation are reproducible in the same patient, and to obtain data concerning the degree of variability in the magnitude of the venous-arterial shunt under various conditions, such as exercise and inhalation of oxygen, which are known to produce striking alterations of the oxygen saturation of arterial blood in patients of this type. Data bearing on these questions have been obtained by means of repeated determinations on the same patient of the variations in oxygen saturation of arterial blood produced by exercise and inhalation of oxygen. This patient (*case 1*) who had a well-compensated congenital cardiac defect and a history of life-long cyanosis has been studied at approximately monthly intervals over a period of one year. These data have been supplemented by information obtained during two cardiac catheterizations carried out on the patient during this period.

It has been found that the oxygen saturations of arterial blood during rest in the supine position and the alterations produced by walking and by inhalation of oxygen were approximately reproducible on each test in this patient. Furthermore, in this and 3 other patients studied, the magnitude of the venous-arterial shunt remained relatively constant under the various conditions imposed.

## METHODS

Oxygen content and capacity of the blood samples were determined by the method of Van Slyke as modified by Roughton, Darling and Root (3). The percentage oxygen saturation was calculated after correction of the oxygen content by subtracting the estimated amount of physically dissolved oxygen (4). Samples of arterial blood were obtained at will during the test procedures

by use of an indwelling arterial needle attached to a stopcock via a polythene tube (5). The alterations in oxygen saturation of arterial blood produced by exercise and inhalation of oxygen were followed continuously by means of a direct-reading oximeter as well as at intervals by Van Slyke analyses of samples of blood withdrawn. The oxygen saturation of samples of blood withdrawn from the heart through the Cournand catheter was determined by means of a whole blood oximeter (6) as well as by direct gasometric analysis of Van Slyke.

The routine procedure utilized for these studies was as follows: The patient lay quietly on a bed in the supine position for 15 or more minutes while the oximeter was attached to an ear. A 2 per cent solution of procaine hydrochloride was infiltrated around the radial artery at the wrist. An indwelling needle was then inserted into this artery and taped in position. A 10-cc. sample of arterial blood was withdrawn into an oiled syringe containing a few milligrams of powdered heparin. The patient then arose and stood quietly on the treadmill for 5 minutes. A second sample of arterial blood was withdrawn and the treadmill was started. A third sample of arterial blood was obtained during the last 60 seconds of the 5½-minute period of walking at 1.7 miles/hour. The patient returned to bed and after the oxygen saturation of arterial blood had stabilized either a 10- or a 14-per cent mixture of oxygen in nitrogen was given by means of a BLB oral-nasal mask (type A-8-B, U. S. Air Corps) for a period of five and a half minutes during the last 60 seconds of which a fourth sample of arterial blood was withdrawn. After restabilization of the oxygen saturation of arterial blood during breathing of air, 100 per cent oxygen was given for a period of 10½ minutes. The fifth sample of arterial blood was obtained during the last 60 seconds of this procedure. To insure that the patient actually inhaled the percentage of oxygen in nitrogen entering the mask system, an excessive flow rate of 25 l/min. was allowed.

In order to determine whether or not the drop in oxygen saturation of arterial blood with exercise might be attributed to an increase in the venous shunt, decreased oxygen content of the venous blood shunted, or to both conditions, the percentage of venous blood by-passing the pulmonary circulation was calculated in each case. This can be done readily if the blood in the pulmonary vein is known to be normally saturated, as the oxygen content of mixed venous blood in the right atrium is obtained with the aid of cardiac catheterization. The formula used for this calculation is as follows:

$$(O_{ra} \times \text{vol.}_{ra}) + O_{pv}(100 - \text{vol.}_{ra}) = O_a \text{ or } \text{vol.}_{ra} = \frac{O_a - (100 \times O_{pv})}{O_{ra} - O_{pv}}$$

When

vol.<sub>ra</sub> = cubic centimeters of right atrial blood by-passing the pulmonary circulation per 100 cc. of left ventricular output

O<sub>ra</sub> = oxygen content 1 cc. of right atrial blood



$O_{pv}$  = oxygen content of 1 cc. of blood from the pulmonary vein

$O_a$  = oxygen content of 100 cc. of arterial blood.

Very simply stated, the oxygen content of the shunted venous portion of blood added to oxygen content of pulmonary oxygenated portion must equal the oxygen content of the arterial sample. The values obtained from such calculations do not entail the reckoning of total systemic or pulmonary flows or the partitioning of the pulmonary flow between the pulmonary artery and collateral channels.

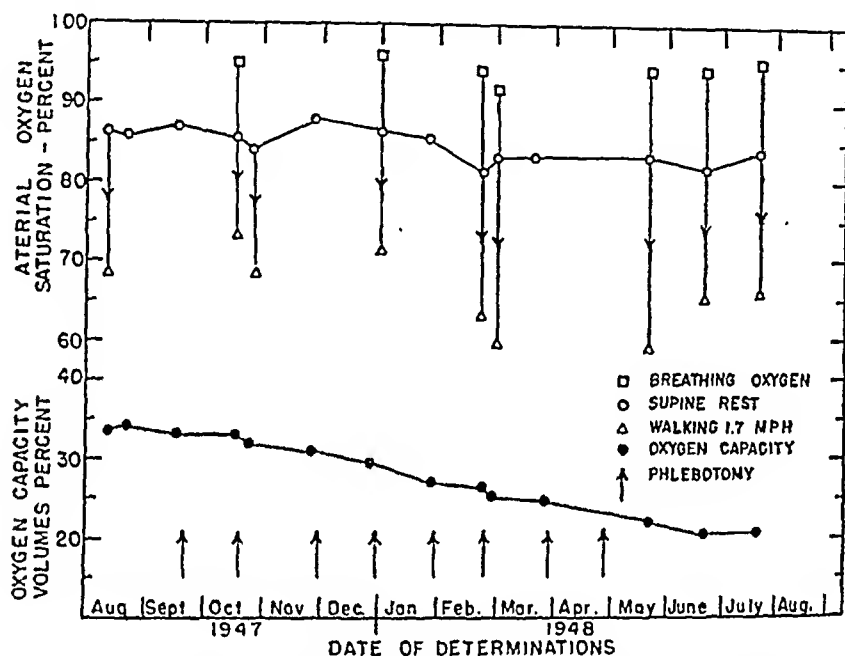


Fig. 1 (Case 1). VALUES FOR THE OXYGEN SATURATION of samples of arterial blood determined by the Van Slyke method. The samples were taken when the oximetric readings had become constant under conditions of rest, breathing either air or 100 per cent oxygen, and practically constant under the condition of exercise. The lower line in the chart shows the change in oxygen capacity related to repeated venesections.

## RESULTS

*Case 1.* During rest in the supine position the oxygen saturation of arterial blood determined by the Van Slyke method averaged 85 per cent and ranged from 81.4 to 88.7 per cent (fig. 1). During the year of observation the oxygen capacity of the blood decreased from 33.6 to 20.9 volumes per cent as a result of monthly phlebotomies. The oxygen saturation of arterial blood determined by the Van Slyke method during the last minute of a 5½-minute period of walking at 1.7 miles per hour averaged 65.5 per cent and ranged from 59.3 to 73.4 per cent. During the breathing of 100 per cent oxygen for a period of 10½ minutes the oxygen saturation of arterial blood at rest increased on the average to 94.5 per cent and ranged from 92.5 to 95.9 per cent. It thus can be

said that for this patient there was a general reproducibility of values for oxygen saturation of arterial blood under similar environmental conditions.

The results obtained by cardiac catheterization of this patient on two occasions are illustrated in figure 2. On the second occasion the patient exercised and breathed different concentrations of oxygen with the catheter in place in the right atrium. First, it is to be noted that the oxygen saturations of arterial and venous blood under resting conditions were practically identical on the two occasions. This existed despite the drop in oxygen capacity of the blood and the increase in the volume of blood flowing through the systemic circulation from 4.8 to 6.0 l/min. The calculated values for the percentage venous shunt were 46 per cent during rest, 52 per cent with exercise, 37 per cent after breathing 100 per cent oxygen and 50 per cent after breathing 10 per cent oxygen. The calculations are as follows:

Rest in supine position	$0.214 \times \text{vol.}_{ra} + 0.29^1(100 - \text{vol.}_{ra}) = 25.5$ $\text{vol.}_{ra} = 46\%$
Walking	$0.135 \times \text{vol.}_{ra} + 0.29^1(100 - \text{vol.}_{ra}) = 21.0$ $\text{vol.}_{ra} = 52\%$
Inhalation of 100% oxygen	$0.229 \text{ vol.}_{ra} + 0.313^2(100 - \text{vol.}_{ra}) = 28.2$ $\text{vol.}_{ra} = 37\%$
Inhalation of 10% oxygen	$0.169 \text{ vol.}_{ra} + 0.238^3(100 - \text{vol.}_{ra}) = 20.2$ $\text{vol.}_{ra} = 51\%$

<sup>1</sup> 98% saturation in lungs is assumed.

<sup>2</sup> 100% saturation + 1.8 cc. of dissolved oxygen is assumed.

<sup>3</sup> 80% saturation in lungs (probable range 70-85%) is assumed.

The drop in the oxygen capacity of the blood during the period of study was accompanied by a progressive decrease in oxygen saturation of arterial blood during rest. If the percentage venous shunt remained constant and the arteriovenous-oxygen difference was also constant, such a decrease might be anticipated because delivery of a given number of cubic centimeters of oxygen to the tissues per 100 cc. of blood will cause a greater decrease in the oxygen saturation of blood of low oxygen capacity than in blood with high capacity. However, the data available do not allow a definite explanation of this finding.

*Case 2.* A patient, a woman 31 years of age, gave a history of progressive cyanosis and fatigability of eight years' duration. The heart was markedly enlarged and the pulmonary artery prominent roentgenoscopically. The electrocardiogram showed evidence of right ventricular hypertrophy. The systolic pressure in the right ventricle was 50 mm. Hg; the pressure in the pulmonary artery was not obtained. The provisional diagnosis was Eisenmenger's complex (ventricular septal defect, an aorta overriding the septal defect and a large pulmonary artery). Walking 1.7 miles per hour for five minutes caused the

oxygen saturation of arterial blood to decrease from 75.6 to 55.7 per cent. The calculated magnitudes of the venous shunt under the various conditions studied were as follows:

Rest in supine position	$0.162 \text{ vol.}_{ra} + 0.288(100 - \text{vol.}_{ra}) = 22.8$
	$\text{vol.}_{ra} = 48\%$
Walking	$0.079 \text{ vol.}_{ra} + 0.288(100 - \text{vol.}_{ra}) = 17.3$
	$\text{vol.}_{ra} = 55\%$
Inhalation of oxygen	$0.196 \text{ vol.}_{ra} + 0.314(100 - \text{vol.}_{ra}) = 25.1$
	$\text{vol.}_{ra} = 53\%$

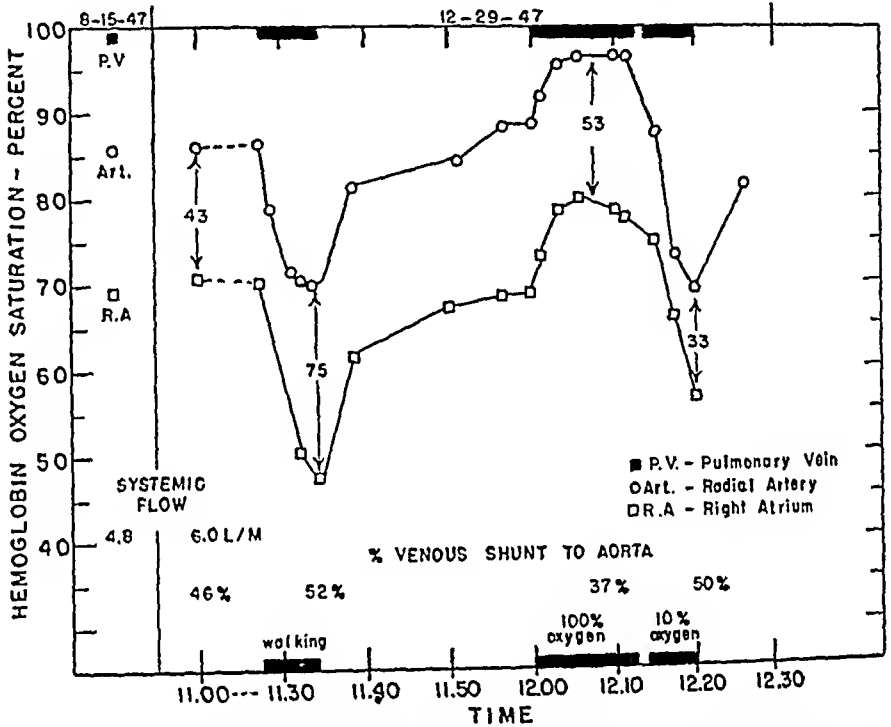


Fig. 2 (Case 1). VALUES FOR THE OXYGEN SATURATION of arterial and mixed venous blood obtained during catheterization of the heart on two occasions. The systemic flow at rest on the two occasions calculated by the Fick principle were 4.8 and 6.0 l/min., respectively. The numbers between the lines showing the oxygen saturation are the differences in oxygen saturation of arterial and venous blood in cc/l. blood.

Case 3. A third patient, a farmer 35 years of age, had been cyanotic since birth but was active and had a relatively good tolerance of exercise. There was a harsh systolic murmur over the sternum and a continuous bruit in the pulmonary region of the type characteristically heard with a patent ductus arteriosus. The cardiac silhouette showed prominence of the left ventricle and the electrocardiogram showed the pattern characteristic of left ventricular hypertrophy. Walking 1.7 miles per hour caused the oxygen saturation of arterial blood to decrease from 77.7 to 47.0 per cent. Following the return of the oxygen saturation to its previous level, the patient breathed 12 per cent oxygen for six and a half minutes during which time the oxygen saturation of

catheterization was performed and the calculations for the percentage venous shunt at rest breathing air and 100 per cent oxygen were as follows:

$$\begin{aligned} \text{Rest in supine position} \quad 0.215 \text{ vol.}_{ra} + 0.323(100 - \text{vol.}_{ra}) &= 26.8 \\ \text{vol.}_{ra} &= 51\% \end{aligned}$$

$$\begin{aligned} \text{Inhalation of } 100\% \text{ oxygen} \quad 0.241 \text{ vol.}_{ra} + 0.350(100 - \text{vol.}_{ra}) &= 29.2 \\ \text{vol.}_{ra} &= 53\% \end{aligned}$$

arterial blood decreased to 69.2 per cent. On the following day, cardiac

*Case 4.* The fourth patient studied by this method was a youth, aged 18 years, who had a severe disability related to pulmonary stenosis and ventricular septal defect (tetralogy of Fallot). In the preliminary studies of exercise, walking at 1.7 miles per hour caused the oxygen saturation of arterial blood to drop from 69 to 37 per cent. The calculated percentage of venous blood by-passing the pulmonary circulation during the breathing of air and 100 per cent oxygen at the time of the cardiac catheterization was as follows:

$$\begin{aligned} \text{Rest in supine position} \quad 0.206 \text{ vol.}_{ra} + 0.327(100 - \text{vol.}_{ra}) &= 24.6 \\ \text{vol.}_{ra} &= 67\% \end{aligned}$$

$$\begin{aligned} \text{Inhalation of } 100\% \text{ oxygen} \quad 0.241 \text{ vol.}_{ra} + 0.351(100 - \text{vol.}_{ra}) &= 27.5 \\ \text{vol.}_{ra} &= 69\% \end{aligned}$$

#### COMMENT

The constancy of the venous shunt may be interpreted as indicating that the severity of the structural defect, often from the practical viewpoint the degree of the pulmonary stenosis, determined the magnitude of the shunt. The actual figures obtained for the magnitude of the venous shunt in each patient show a constancy which is remarkable considering the possible errors in the values obtained for the various samples of blood. Further investigations may show considerably greater variation in the calculated shunt without contradicting the general conclusion that the amount of blood by-passing the pulmonary circulation is relatively constant. It is probable that there are minor fluctuations in the magnitude of the venous shunt during the respiratory cycle (7) or perhaps during the heart beat; however, the average percentage of the blood by-passing the pulmonary circulation over a period of several minutes tends to remain the same. These results are in accord with our observation that variations in the systemic blood pressure and assumedly systemic peripheral resistance produced by tetraethyl ammonium ion and neosynephrine caused no significant change in oxygen saturation of the arterial blood of a patient who had tetralogy of Fallot. Breathing under positive pressure which might be thought to affect pulmonary peripheral resistance has failed to cause any decrease in oxygen saturation of arterial blood of patients who have tetralogy of Fallot.

With profound drops in systemic blood pressure observed on occasion in the operating theater, we have observed precipitous decreases in the oxygen saturation of arterial blood. Under such circumstances it is probable that the drop in oxygen saturation is caused by a marked increase in the venous shunt related to the greatly lowered systemic peripheral resistance.

In the first case the calculated venous shunt decreased during the breathing of 100 per cent oxygen. This suggests that the pulmonary resistance of this patient decreased with the breathing of 100 per cent oxygen. This observation may be parallel to the observation of Motley and co-workers (8) that breathing 10 per cent oxygen increased the pulmonary resistance. The results in the other three cases give no support to such a possibility.

### SUMMARY

Reproducible values for the oxygen saturation of arterial blood during rest, exercise and breathing 100 per cent oxygen have been obtained over a year's time in one case of congenital intracardiac venous-arterial shunt. The magnitude of venous shunts has been found to remain relatively constant during these varying conditions in each of 4 patients with congenital cardiac disease of cyanotic type. The decrease in oxygen saturation of arterial blood with exercise is related to a decrease in the oxygen content of the shunted venous blood in the patients studied.

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## *Normal Oxygen Saturation of Arterial Blood During Inhalation of Air and Oxygen*

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ROUGHTON AND HIS CO-WORKERS (1) in 1944 reported that there was a systematic error of approximately 2 per cent in the determination of the oxygen capacity of blood by the tonometer method, which could be avoided by use of a modification of the method described by Sendroy (2) for determination of the oxygen capacity of blood by equilibration in the Van Slyke apparatus. Because of the error in the tonometer method, the average value of 95 per cent for the normal oxygen saturation of arterial blood, determined by the standard Van Slyke gasometric technic (3), was 2 to 3 per cent too low and the resulting value of the partial pressure of oxygen in arterial blood (arterial  $pO_2$ ) calculated on the basis of this value was approximately 80 mm. Hg instead of approaching the 100 mm. Hg level which would be expected if the alveolar-to-arterial oxygen pressure gradient were very small. These findings have been confirmed in several different laboratories using different methods (4-7) and in this laboratory (8) by carrying out simultaneous analyses on a series of samples of blood by both the tonometer and Roughton technic. Results of an adequate series of determinations of oxygen saturation of arterial blood of normal human beings by the methods described by Roughton have not been reported.

In the course of calibration studies on the Millikan oximeter and its modifications (9-11) more than 200 determinations of oxygen saturation of arterial blood have been made by this method in normal subjects who were breathing air, oxygen and various mixtures of oxygen and nitrogen. These data are reported herein to aid in the establishment of the average and range of arterial saturations encountered in normal human beings during the breathing of air and 100 per cent oxygen. Besides their physiologic significance, those values are of importance in the assessment of pulmonary and cardiac abnormalities (12-16).

### METHODS

Twenty-nine normal (volunteer) subjects (27 males and 2 females), ranging in age from 17 to 54 years, were used in these studies. Each subject lay quietly on a bed for 15

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or more minutes during which time the carpieces of the oximeter were attached to the ears and 1 to 2 cc. of 2 per cent procaine hydrochloride was infiltrated around the radial artery at the wrist. A specially ground no. 20-gauge hypodermic needle was inserted into the radial artery and attached to an arterial sampling device so that samples of blood could be obtained at will throughout the course of the procedure (17). Samples of blood were collected in a syringe containing a few mg. of powdered heparin and sufficient mineral oil to fill the dead space of the syringe. After the withdrawal of the sample of blood, a small quantity of clean mercury was aspirated into the syringe to act as a mixing bead; the syringe was capped tightly and stored in a shaded ice bath. All analytical procedures were completed within five hours of withdrawal of the samples of blood.

Oxygen and the various oxygen-nitrogen mixtures were administered by means of a BLB oronasal mask (Army type A8-B) at rates of flow in excess of 26 l/min. for periods of five or more minutes.

The oxygen and carbon dioxide contents of 1 cc. duplicate samples of blood were determined by the gasometric method of Van Slyke (3). Oxygen capacities were determined manometrically after equilibration of 1 cc. samples of blood by the method of Sendroy (2) as modified by Roughton and his co-workers (1). The standard deviations of the differences between 54 duplicate determinations of oxygen content, oxygen capacity and oxygen saturation were 0.1 volume per cent, 0.1 volume per cent and 0.5 per cent saturation, respectively.

The corrections for physically dissolved oxygen were calculated from the equation of Sendroy and his co-workers (18). It was assumed that the arterial  $pO_2$  was 100 mm. Hg when the subject was breathing air and was the barometric pressure minus 86 when he was breathing oxygen.

## RESULTS

The oxygen saturation of the arterial blood of 29 normal subjects breathing air averaged 97.9 and ranged from 94 to 101 per cent (table 1). The standard deviation of the individual values was 1.4 per cent. Taking the mean  $\pm 2$  standard deviations to include 95 per cent of the cases, we may say that for any individual determination on a normal subject there is approximately a 95 per cent chance of falling within the limits of 95 to 101. This range of normal values is considerably greater than the inherent variability of the analytical procedures.

After inhalation of oxygen for an average period of 12 (5-33) minutes the oxygen saturation of arterial blood of the 20 subjects studied averaged 99.1 and ranged from 97 to 101 per cent (table 1).

Since the arterial  $pO_2$  when the subject breathes pure oxygen for more than five minutes approaches the barometric pressure minus the alveolar tension of carbon dioxide and water vapor (13), it can be assumed that the hemoglobin of arterial blood is completely saturated under these conditions (altitude = 1,040 ft., av. barometric pressure = 732 mm. Hg). That the average oxygen saturation of arterial blood during the breathing of oxygen is significantly less than 100 per cent indicates that there must be a systematic error in either the analytical procedures or in the assumptions on which the calculations of oxygen saturation of arterial blood are based, or both.

The assumptions which are most probably in error concern the calculation of the physically dissolved oxygen in arterial blood during inhalation of 100 per cent oxygen. These are: 1) that the solubility coefficient of oxygen determined on whole beef blood (Sendroy and associates, 18) applies to human blood and 2) that the arterial pO<sub>2</sub> during breathing of oxygen for more than five minutes is equal to the alveolar pO<sub>2</sub> which approaches the barometric pressure minus the sum of the alveolar tensions of carbon dioxide, water vapor and the residual nitrogen, assumed to be 36, 47 and 3 mm. Hg, respectively (19).

It would be possible to estimate the magnitude of the error resulting from these assumptions if there were no systematic error in the determination of the oxygen content and capacity of arterial blood during inhalation of oxygen since, under these conditions, the physically dissolved oxygen is equal to the

TABLE 1. GASOMETRIC STUDIES OF ARTERIAL BLOOD WITHDRAWN FROM NORMAL SUBJECTS DURING INHALATION OF AIR AND 100 PER CENT OXYGEN

INHALATION OF:	SUBJECTS	ARTERIAL SAMPLES	VOLUMES PER CENT				% OXYGEN SATURATION <sup>1</sup>
				Total carbon dioxide content	Total oxygen content	Oxygen capacity	
Air	29	46	Average...	48.5 ± 0.5 <sup>2</sup>	19.5 ± 0.3	19.6 ± 0.3	97.9 ± 0.3
			Range.....	42.8 to 53.2	17.0 to 23.1	17.0 to 23.1	94.1 to 101.0
Oxygen	20	35	Average...	47.9 ± 0.4	21.1 ± 0.3	19.3 ± 0.3	99.1 ± 0.2
			Range.....	44.4 to 50.8	19.0 to 24.1	17.0 to 22.5	97.3 to 101.1

<sup>1</sup> Calculated after correction of the oxygen content by subtraction of amount of physically dissolved oxygen (0.3 and 2.0 vol. % during inhalation of air and oxygen respectively). <sup>2</sup> The number following the ± sign is the standard error of the mean; n = 29 and 20 for air and oxygen values respectively.

oxygen content minus the oxygen capacity. The values for the physically dissolved oxygen determined in this manner averaged  $1.83 \pm 0.03$  and ranged from 1.4 to 2.2 volumes per cent. This value is significantly less (p value < 0.001) than the average calculated value of 1.95 (table 2).

It has not been established whether this difference is due to errors in the calculated values for physically dissolved oxygen or due to systematic analytical errors. Available evidence indicates, however, that this error arises from the fact that during inhalation of oxygen, the arterial pO<sub>2</sub> is significantly lower than the alveolar pO<sub>2</sub> (6, 13). The average difference between alveolar and arterial oxygen pressures which would be required to produce the difference of  $0.12 \pm 0.03$  volume per cent in the determined and calculated values for physically dissolved oxygen has been calculated to be  $40 \pm 9$  mm. Hg. (table 2) (18).

Perhaps the most likely source of analytical error in the determination of the oxygen saturation of blood is in the determination of the oxygen capacity



(1, 20). The magnitude of this possible error could be estimated if it were assumed that there were no systematic errors in the determination of oxygen content and the calculation of physically dissolved oxygen, since the oxygen capacity, under these conditions, is equal to the oxygen content minus the amount of oxygen in physical solution (20). It is of interest to determine the

TABLE 2. COMPARISON OF THE CALCULATED AND DETERMINED VALUES FOR PHYSICALLY DISSOLVED OXYGEN IN ARTERIAL BLOOD DURING INHALATION OF OXYGEN

	PHYSICALLY DISSOLVED OXYGEN VOL. %			CALCULATED PRESSURE DIFFERENCE ( $\Delta pO_2$ ) <sup>3</sup> MM. Hg
	Calculated $dO_2$ <sup>1</sup> (Sendroy and co-workers) <sup>2</sup>	Determined $dO_2$ <sup>2</sup>	Difference ( $\Delta dO_2$ ) Arterial oxygen deficit	
Average.....	$1.95 \pm 0.004^4$	$1.83 \pm 0.03$	$0.12 \pm 0.03$	$40 \pm 9$
Range.....	1.92 to 2.01	1.4 to 2.2	-0.27 to 0.58	-90 to 190
p value.....			<0.001	<0.001

<sup>1</sup> Calculated  $dO_2 = 100 (B-86) \propto 38^\circ/760$ . <sup>2</sup> Determined  $dO_2 =$  total  $O_2$  content minus  $O_2$  capacity. <sup>3</sup> Calculated difference in oxygen pressures in alveoli and arterial blood:  $\Delta pO_2 = (760 \Delta dO_2) \div (100 \propto 38^\circ) \propto 38^\circ = 0.0209 + 0.000108$  (vol. % oxygen capacity). <sup>4</sup> The number following the  $\pm$  sign is the standard error of the mean,  $n = 35$ ; 20 subjects.

TABLE 3. GASOMETRIC STUDIES OF SAMPLES OF ARTERIAL BLOOD WITHDRAWN FROM 16 NORMAL SUBJECTS DURING INHALATION OF BOTH AIR AND 100 PER CENT OXYGEN; AVERAGE VALUES; 20 DETERMINATIONS<sup>1</sup>

DURING INHALATION OF:	TOTAL CONTENTS VOL. %		OXYGEN CAPACITY VOL. %		PER CENT OXYGEN SATURATION <sup>4</sup>	
	CO <sub>2</sub>	O <sub>2</sub>	In vitro technic	In vivo technic	In vitro technic	In vivo technic
Air.....	$49.0 \pm 0.5^3$	$19.0 \pm 0.3$	$19.2 \pm 0.4$	$19.0^4$	$97.8 \pm 0.4$	$98.6 \pm 0.4$
Oxygen.....	$48.0 \pm 0.5$	$21.0 \pm 0.4$	$19.2 \pm 0.4$	$19.0 \pm 0.4$	$99.3 \pm 0.2$	$100^4$
Difference.....	$1.0 \pm 0.2$	$2.0 \pm 0.08$	$0.01 \pm 0.02$		$1.5 \pm 0.4$	
p value.....	<0.001	<0.001	<0.60		<0.001	

<sup>1</sup> Determinations were excluded in which the arterial oxygen capacities obtained during inhalation of air and of oxygen differed by more than 0.1 vol. %. <sup>2</sup> Calculated after correction of the oxygen content by subtraction of amount of physically dissolved oxygen (0.3 and 1.96 vol. % during inhalation of air and of oxygen respectively). Av. barometric pressure: 734 (720-743) mm. Hg. <sup>3</sup> The number following the  $\pm$  sign is the standard error of the mean,  $n = 16$ . <sup>4</sup> Assumed values.

oxygen saturation of arterial blood of normal subjects when this technic of *in vivo* equilibration is used to establish the oxygen capacity (20). The oxygen saturation of arterial blood of 16 normal subjects when breathing air determined by this procedure averaged  $98.6 \pm 0.4$  and ranged from 96.7 to 100.6 per cent. This value was significantly higher (p value <0.001) than the aver-

age saturation of 97.8 per cent determined by the gasometric technic of Roughton and his co-workers (1) (table 3).

The increase in total oxygen content produced by breathing oxygen averaged  $2.0 \pm 0.08$  volumes per cent. The proportion of this added oxygen in physical solution and in combination with hemoglobin cannot be ascertained from the available data.

#### COMMENT

An oxygen tension of 150 mm. Hg is generally considered sufficient to produce complete saturation of the hemoglobin in whole blood. Since inhalation of oxygen at sea level produced arterial oxygen tensions in excess of 600 mm. Hg (13), it can be assumed that the oxygen saturation of arterial blood is 100 per cent under these circumstances. The average value of  $99.1 \pm 0.2$  per cent obtained in these studies is proof that there was a systematic error in this determination. Available data (6, 13) indicate that the major source of error arises in the calculation of physically dissolved oxygen during the breathing of oxygen by the conventional method (20) in which equilibrium between alveolar and arterial oxygen tensions is assumed. On this basis the determined oxygen content during oxygen breathing (av. barometric pressure, 732 mm. Hg) was corrected for the amount of physically dissolved oxygen by subtracting 1.96 volumes per cent. The data obtained herein would be inherently consistent if this value were assumed to be 1.83 volumes per cent. By a similar procedure but less well-established methods Preston and Ordway (21) have obtained a value of 1.09 volumes per cent.

The average figure of 97.9 for normal oxygen saturation of arterial blood determined by the Roughton technic is not significantly different from that reported by Comroe and Walker (20). However, it is 4.8 per cent higher than the value found for children by Preston and Ordway (21).

The finding that the average oxygen saturation during inhalation of air as determined by the *in vivo* equilibration technic was  $0.8 \pm 0.2$  per cent higher than the value determined by the *in vitro* technic is at variance with the results of Comroe and Walker (20). Identity of the saturation values determined by these two technics indicates that during inhalation of oxygen the difference between the oxygen pressures in the alveolar air and arterial blood is insignificant. The careful studies of Berggren (13) indicate that this value averages 11 mm. Hg in normal seated subjects and 42 mm. Hg in patients at rest in bed but with otherwise normal cardiorespiratory systems. Fasciola and Chiodi (6) using somewhat different methods obtained an average difference in arterial-alveolar tensions of 36 mm. Hg. The data reported herein would be inherently consistent, if it were assumed that there was an average difference in oxygen tension of 40 mm. Hg between the alveoli and the arterial blood of normal sub-

jects during inhalation of oxygen. This difference could be explained by assuming that in the supine resting position approximately 2 per cent of the blood flow through the heart by-passes aerated alveoli.

Following the work of Matthes (22, 23) several attempts have been made to establish the normal value for oxygen saturation of arterial blood by determining the increase in saturation produced by the breathing of oxygen (9, 20, 24). This method is based on the assumption that the oxygen saturation of arterial blood is linearly related to the logarithm of the difference in relative

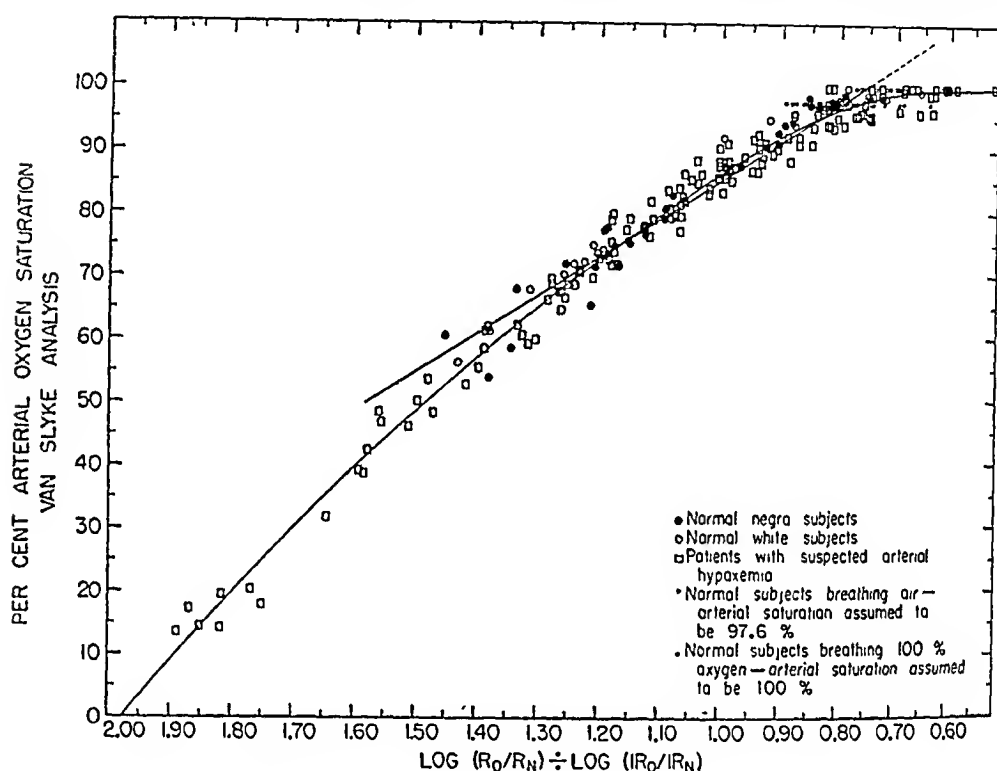


Fig. 1. EMPIRICAL CALIBRATION CURVE of a direct reading oximeter earpiece (10, 11). The curved lines represents the closest visual fit to the 208 experimental points. The straight line represents the closest visual fit to the points between 50 and 100% saturation, assuming that the oxygen saturation of the blood is linearly related to the ratio of the logarithm of transmission of red and infrared light through the ear.

transmission of red and infra-red light by the ear (25-27). Extensive gasometric-calibration studies carried out on the Millikan oximeter (9), a direct reading oximeter (10, 11), and an *in vitro* whole-blood oximeter (28) indicate that this is not the case. If, in the case of the direct reading oximeter, a linear relationship is assumed, the increase of saturation produced by breathing oxygen as determined photo-electrically was 4 per cent as compared to the 1.2 per cent saturation determined by manometric methods (fig. 1). This photo-electric value would indicate that the normal oxygen saturation of arterial blood was 96 per cent, a value which is in agreement with that of Comroe and Walker determined with the Millikan oximeter.

It is of interest that the average carbon dioxide content of arterial blood averaged  $1.0 \pm 0.2$  volume per cent less during inhalation of oxygen through a BLB mask than during breathing of air without a mask (table 3). This may indicate that normal subjects exhibit a slight tendency to hyperventilate when breathing through an oxygen mask.

#### SUMMARY

The oxygen saturation of arterial blood, determined in 29 subjects by the technic of Roughton and his co-workers averaged  $97.9 \pm 0.3$  per cent when the subjects were breathing air and were at rest in bed. The variability of the individual values was such that a range of saturation from 95 to 101 per cent would likely include 95 per cent of the values obtained on normal subjects. Oxygen saturation of arterial blood was measured in 16 of these subjects under the same conditions by an *in vivo* equilibration technic described by Comroe and Walker. An average value of  $98.6 \pm 0.4$  per cent was obtained. Oxygen saturation of arterial blood was determined on 20 subjects during inhalation of oxygen. The average value of  $99.1 \pm 0.2$  per cent which was obtained indicates that there was a systematic error in the calculation of the oxygen saturation of arterial blood under these circumstances. It is believed that this error as well as the difference in results obtained by the *in vitro* and *in vivo* equilibration technics arise, at least in part, from the calculated correction for physically dissolved oxygen when the difference in the alveolar-arterial oxygen tensions is assumed to be insignificant.

The data indicate that the average amount of physically dissolved oxygen during inhalation of oxygen was  $1.83 \pm 0.03$  volumes per cent as compared to 1.95 volumes per cent obtained by the conventional method of calculation. This difference is consistent with a difference in alveolar-arterial oxygen tensions during oxygen inhalation of  $40 \pm 9$  mm. Hg. A difference in tension of this magnitude could be explained by the assumption that approximately 2 per cent of the blood flow through the heart by-passes aerated alveoli.

Gasometric-calibration data on a direct reading oximeter earpiece are presented and data on the Millikan oximeter and an *in vitro* whole-blood oximeter are cited which indicate that the relationship between the oxygen saturation of blood and the logarithm of the oximeter galvanometer deflection is nonlinear. Therefore, the increase in saturation produced by inhalation of oxygen as determined by the standard oximeter scale cannot be used as an accurate indication of the normal oxygen saturation of arterial blood.

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# *Physiological Reactions to Cold and Their Effects on the Retention of Acclimatization to Heat<sup>1</sup>*

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**A**CCLIMATIZATION MAY BE DEFINED as the process of adapting to a new environment in such a way that tolerance and ability to function in a new environment are increased. Acclimatization to heat (1-5) and to anoxia (6) have been convincingly demonstrated. In contrast, only rather equivocal evidence for the existence of acclimatization to cold has been presented.

The approach to the problem of cold acclimatization has been influenced by findings in heat acclimatization, where considerable work has been done on cardiovascular adjustments. The blood pressure rises initially with cold exposure but then falls (7). There is diminished peripheral blood flow as indicated by fall in skin temperature, serial infrared photographs of peripheral blood vessels, and direct plethysmography of limbs (7). This reduced peripheral flow decreases the conductivity of the skin (8), and some studies have shown a smaller fall in rectal temperatures on repeated cold exposures (9), presumably due to this heat-conserving mechanism. Accompanying and possibly aiding peripheral vasoconstriction, some investigators have found decreased plasma volume (2), hemoconcentration (2, 10) and reduced cardiac output (7). The reduction in plasma volume and the hemoconcentration are probably accomplished by means of the well-known diuresis which occurs in the cold (10). Cold exposure produces both a negative water balance and a negative chloride balance (11). It has not been shown conclusively that any of these adjustments increase man's tolerance to cold.

Cardiovascular adjustments during acclimatization to heat have been well established by the data of numerous workers. The amount of rise in pulse rate, pulse pressure and body temperature during work at a fixed rate in the heat is reduced with successive heat exposures (1, 4, 12, 13). The rate of sweating increases, producing lower skin temperatures and permitting greater heat dissipation per unit of blood carried to the body surface (6, 14, 15). The plasma volume is increased initially (2, 16) which permits greater cardiac output at a given pulse rate (7) and permits greater peripheral vasodilatation without circulatory collapse. In cross-acclimatization studies, water and chloride balances tend to be positive in the heat relative to the cold (18).

The present studies were undertaken to investigate the mechanism of acclimatization to cold and to ascertain the loss of acclimatization in heat-acclimatized men subjected to prolonged cold exposures, utilizing cardiovascular and metabolic indices. The effects of these

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environmental stresses upon the hormonal regulatory mechanisms, namely, the adrenal cortex and the thyroid, were studied also, but these observations will be reported elsewhere (19).

#### EXPERIMENTAL DESIGN

After an initial period of physical conditioning, 3 healthy, unacclimatized, white males ranging in age from 20 to 26 years were subjected successively to 19 intermittent periods of heat exposure, 14 intermittent exposures to cold, 5 re-exposures to heat and finally, after an interval of five weeks, with no physical conditioning or exposures to extreme heat or cold, 3 re-exposures to heat. Throughout the various experimental periods, measurements of cardiovascular function, metabolic activity, fluid and chloride balance were made in order to evaluate the relationship of alterations in these physiological functions to the environmental stress encountered by the test subjects.

The weekly experimental period began with the evening meal on Sunday and ended on the following Friday afternoon when the test subjects had completed the day's exposure in the climatic chamber. During this five-day period, food and fluid intake for each test subject was recorded on a daily basis beginning with the evening meal. No effort was made to control the quantity of food or fluid consumed by the test subjects except that no solid food was allowed after 7:00 P.M., and no fluids were permitted after 10:00 P. M. Total 24-hour urine collections were made on each man for every day of the experimental period.

In order to insure basal conditions for metabolic tests and blood volume studies, the men retired at 11:00 P.M. in their special barracks which were outfitted with the equipment required to conduct these tests. The men were awakened at 7:00 A.M., permitted to void, and then they were kept in basal condition during the next three hours while various tests were performed. Following the conclusion of this period the men were fed a large breakfast prior to entering the climatic chamber for the day's exposure.

During the five-week interval when the men were not exposed to either extreme heat or cold, no tests were conducted and they performed their usual military duties.

#### EXPERIMENTAL CONDITIONS IN THE CLIMATIC CHAMBERS

Physical conditioning was accomplished by having the men walk seven miles in two hours on a treadmill, daily for 10 days, in a constant-temperature room maintained at 68°F. with a relative humidity of 40 to 50 per cent and a wind velocity of 3 m.p.h. During the exercise period the men were clad in light clothing.

The hot room exposures were carried out in a climatic chamber maintained at 107°F. D.B. (89°F. W.B.) with a wind velocity of 3 m.p.h. Each exposure

lasted for five and one-quarter hours during which time each man walked on the treadmill at 3.5 m.p.h. on the level for two periods, of 60 and 30 minutes. During the remainder of the time in the chamber, the men sat quietly. Each man wore an athletic supporter, cushion sole socks and gymnasium boots plus skin and rectal thermocouples, and cotton drawers to reduce chafing while walking on the treadmill. Each day before entering the chamber, control values of pulse rate, rectal and skin temperatures were taken for each man. The men were weighed upon entering the chamber, and hourly thereafter. Fluid in the form of 0.1 per cent saline was supplied after each weighing to replace the weight lost through sweating so that each man's weight was maintained constant for each day's exposure. Readings of pulse rate, skin and rectal temperatures were taken every 15 minutes while sitting, and every 7½ minutes on the treadmill. The first man walked on the treadmill one hour after entering the chamber and the other test subjects exercised one and two hours later. Expired air samples were collected twice during the 60-minute exercise period with each collection period lasting 10 minutes. At the conclusion of the exercise period, the man was wiped dry of perspiration and weighed. During the next 15 minutes pulse rate, skin and rectal temperatures were recorded every 5 minutes. After this period of 15 minutes, these measurements (excepting weight) were made every 15 minutes until the man again exercised on the treadmill for another 30 minutes. During this exercise period and the subsequent 15 minutes after exercise, measurements were made as during the initial periods.

The cold room exposures were conducted in a climatic chamber maintained at  $-20^{\circ}\text{F.}$  with a wind velocity of 3 to 4 m.p.h. Each man wore, in addition to skin and rectal thermocouples, a heavy Arctic clothing assembly made up of standard Army items. Each exposure lasted for five hours during which time the men sat quietly except during periods of exercise on the treadmill. Skin and rectal temperatures were recorded every 10 minutes. A man was exercised when his toe or knee temperature had fallen to  $45^{\circ}\text{F.}$  He then walked on the treadmill at the rate of 3 m.p.h. on the level for one or more periods of 10 minutes until his toe or knee temperature had risen to  $50^{\circ}\text{F.}$  or more. This procedure eliminated the danger of frostbite or related phenomena and at the same time allowed only the minimum amount of heat production so that the maximal cold stress possible under these experimental conditions could be maintained. Each man was weighed on the tripod balance before and after each chamber exposure.

#### EXPERIMENTAL METHODS

Skin temperature was measured with five thermocouples constructed of no. 30 B & S copper-constantan, which were connected to a Brown electronic potentiometer (flight test model). The thermocouples were attached to the



skin with small pieces of adhesive tape. They were located on the medial aspect of the distal phalanx of the left index finger; on the abdomen, one inch to the left of the umbilicus; the lateral aspect of the left mid-thigh; the left lower leg immediately below the patella; and the medial aspect of the left great toe. Rectal temperature was recorded by a no. 30 B & S copper-constantan thermocouple mounted at the tip of a no. 14 soft rubber catheter which was inserted between four and five inches above the internal rectal sphincter. The thermocouple was connected to a Leeds and Northrup potentiometer (Model 8662). Pulse rates were counted manually for 30 seconds.

Caloric expenditure during exercise was determined by collecting expired air samples into 600-liter Tissot spirometers, analyzing the samples for oxygen and carbon dioxide and then computing the metabolic rate (20). Total blood and plasma volumes were measured by the T-1824 blue dye method of Gibson and Evans (21). Simultaneously, 'available fluid' (thiocyanate space) was determined by the procedure of Laviates *et al.* (22), utilizing an intravenous injection of 10 cc. of a 5 per cent solution of sodium thiocyanate. Blood thiocyanate was measured by Bowler's method (23). Total plasma proteins were obtained by the copper sulfate method of Phillips *et al.* (24).

Rates of sweating for the test subjects during the heat exposures were calculated from hourly weighings on the tripod balance, which had an accuracy of  $\pm 10$  grams. The men were wiped dry before each weighing.

Sodium chloride intake was calculated from the daily dietary intake using a table of standard portions (25), plus daily weighings of each test subject's salt shaker. During the heat exposures, the amount of salt given as 0.1 per cent saline was not added to the daily chloride intake, since it was felt that it was nearly balanced by the chloride lost in sweat. No actual measurement was made of the amount of chloride lost through sweating. Urinary chloride excretion was measured daily (17).

#### EXPERIMENTAL RESULTS

*Cardiovascular and Metabolic Adjustments During Heat Stress.* The classical changes associated with acclimatization to heat were observed in the three test subjects during the first 7 to 10 days of the initial, 19 heat exposures (107°F. D.B., 89°F. W.B., wind 3 m.p.h.). The pulse rate, skin and rectal temperatures, and caloric expenditure, during exercise in the heat, all showed a gradual decline, and the rate of sweating increased (fig. 1). In every instance the test subjects' data showed identical trends, so data are presented as averages of the three men. It will be noted that once acclimatization had been attained by the men, subsequent exposures did not produce better performances with respect to the physiological indices, but rather the men maintained their level of performance throughout the period of exposures subsequent to the time of acclimatization.

Utilizing these same indices during the period of 5 re-exposures to heat following 14 intermittent exposures to cold, it was revealed that most of the acclimatization to heat had been retained. The performances of the men during the first two days of this period were comparable with those observed during the later stages of the initial period of acclimatization. Following 2 exposures, however, all of the subjects showed complete re-acclimatization (fig. 1). Thus, the effect of the intervening cold stress apparently was not detrimental to the maintenance of heat acclimatization.

When the men were re-exposed again to heat after a five-week rest period with no environmental stress, they showed considerable loss of acclimatization on the first day. This may have been due to the lack of physical conditioning during the rest period since they appeared to be fully re-acclimatized on the second and third days of re-exposure (fig. 1).

*Cardiovascular and Metabolic Adjustments During Cold Stress.* There was a definite trend toward more rapid and more marked peripheral vasoconstriction with successive cold exposures, which was demonstrated by a more rapid fall in toe temperatures to the critical level of 45°F. at which the men were walked on the treadmill (fig. 1, table 1). This trend was statistically significant in subjects *E* and *P*, but not in subject *H*. There was no evidence of adaptation noted in other skin temperatures, in rectal temperature or in the time of the onset of shivering. The latter usually occurred only during and after walking on the treadmill, coincidentally with a slight fall in rectal temperature presumably caused by a loss of heat into the extremities.

*Alterations in Body Water During Heat and Cold Stress.* Blood, plasma and 'available fluid' volumes together with total plasma proteins and hematocrits were determined simultaneously three times during the conditioning period, following 1, 3, 5, 8, 12 and 17 heat exposures, following 1, 3, 5, 8 and 12 cold exposures and after 1 and 4 re-exposures to heat. There were no statistically significant changes in blood, plasma or 'available fluid' volumes during any of the experimental periods. Plasma protein levels and hematocrits, however, demonstrated a definite tendency toward hemodilution in the heat and hemoconcentration in the cold (table 2, fig. 2).

*Water and Chloride Balances During Heat and Cold Stresses.* Fluid and chloride balances were consistently negative in the cold relative to the first heat period, and only slowly became positive again on re-exposure to heat, although the pulse and metabolic rates, rectal temperature and subjective reactions of the men indicated that they were still well acclimatized to heat (fig. 2). Body weight tended to fall during the cold exposures but, like the water and chloride balances, was slow to change upon re-exposure to heat.

Rate of sweating was distinctly reduced during the re-exposures to heat, apparently without detriment to the men's heat tolerance (fig. 1). The conservation of water and chloride in the heat was effected principally by marked

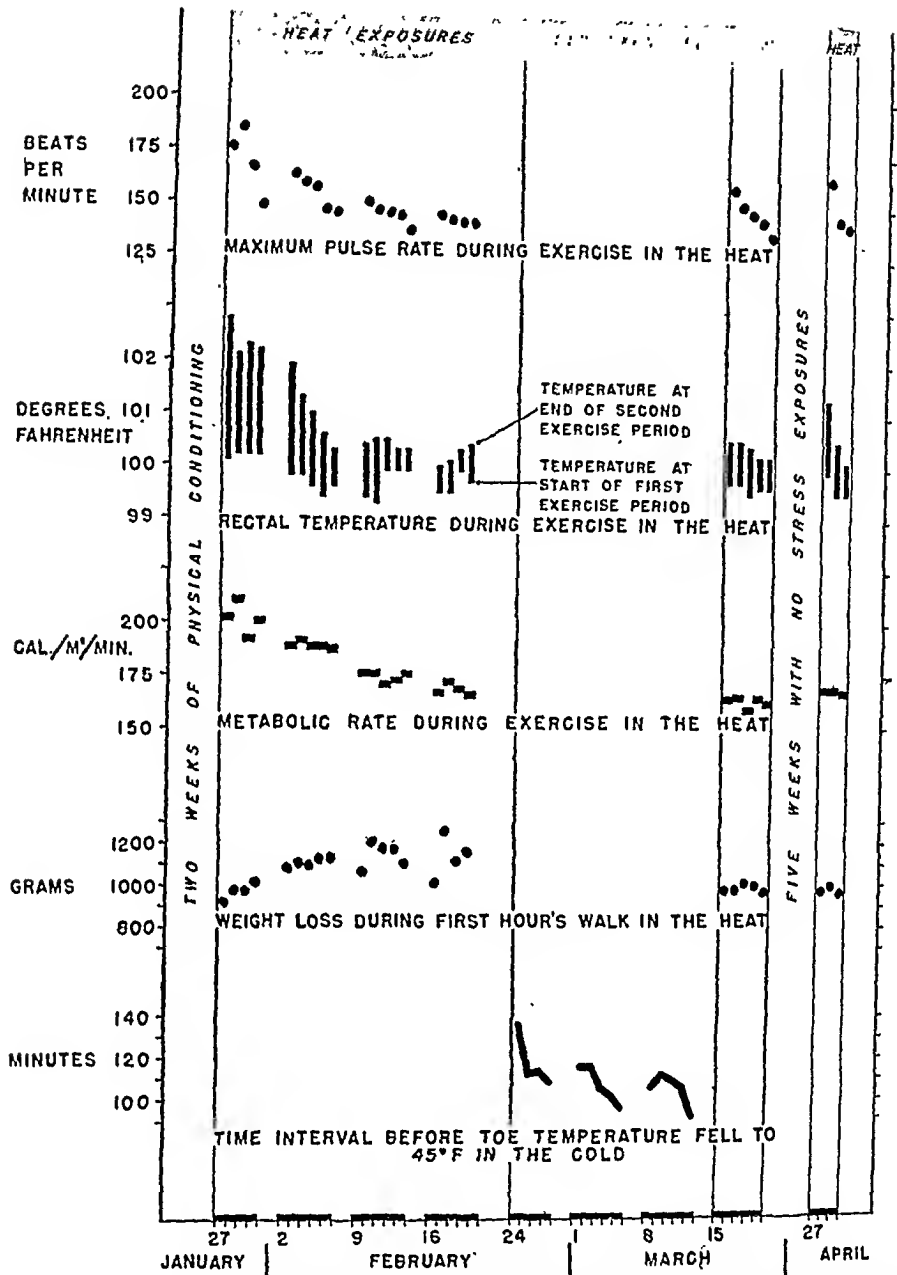


Fig. 1. Average data of 3 test subjects exposed intermittently to heat and cold stress, show pulse rate, rectal temperature, metabolic rate during exercise and sweat output measured by weight loss in the heat. Average time before toe temperature fell to 45°F. in the cold is also shown.

TABLE 1. STATISTICAL ANALYSIS OF DATA SHOWING TIME IN MINUTES BEFORE TOE TEMPERATURE FELL TO 45° F. DURING EACH COLD EXPOSURE

SUBJECT	R = RATE OF DECREASE/EXPOS.	Z = MEASURE OF DIFF. OF VARIABILITY	z = STANDARD DEVI- ATION OF Z	TREND	STATISTICALLY SIGNIF.
E	0.662	0.80	0.32	2.6	Yes
H	0.340	0.35	0.30	1.19	No
P	0.841	1.22	0.30	3.00	Yes

reduction in urinary output, especially during the early days of the first heat exposure. A distinct diuresis and increased chloride excretion existed throughout the cold period producing the negative water and chloride balances. There is suggestive evidence that the negative water and chloride balances were

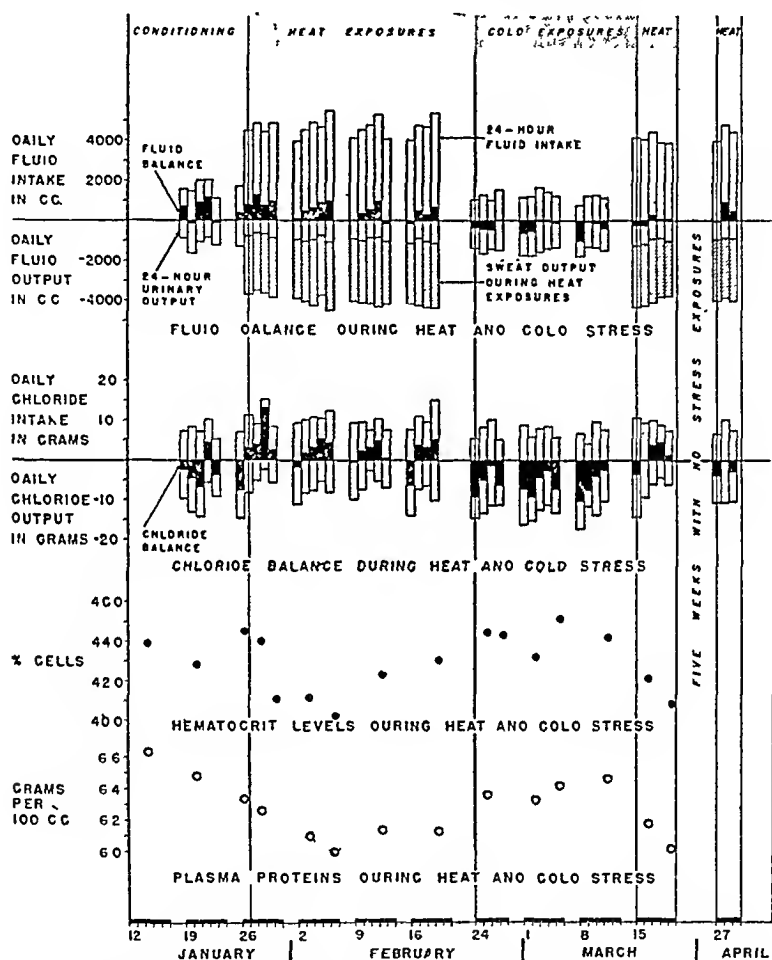


Fig. 2. Average data of 3 test subjects exposed intermittently to heat and cold stress are presented for fluid and chloride balance, hematocrit and plasma protein values.

partially reversed over the weekends during the cold exposure period, particularly in *subject E*, in whom there were markedly negative balances on nearly every Monday and an increased body weight on the same day.

#### DISCUSSION

It has generally been supposed that adjustments made by the body to heat would be detrimental to well-being in the cold and would be largely reversed by

exposure to cold. The more severe the extremes to which the man is subjected, the more dramatic should be the compensating shifts in homeostasis. Retention of heat acclimatization after a period of exposure to no stress has been reported (26). The present study, however, is the first demonstration that retention of heat acclimatization can persist even with fairly severe cold exposures intervening. This finding suggests that acclimatization to cold, if it exists, is accomplished at least in part by different mechanisms from those involved in heat acclimatization, which do not necessitate the reversal of the physiological changes of heat acclimatization. Another possible explanation is that many of the fundamental changes which occur are the same in both types of acclimatization, and one may actually reinforce the other.

TABLE 2. MEAN VALUES, WITH STANDARD DEVIATIONS, FOR BLOOD, PLASMA AND 'AVAILABLE FLUID' VOLUMES, HEMATOCRITS AND PLASMA PROTEINS IN MEN EXPOSED TO HOT AND COLD ENVIRONMENTAL STRESSES

SUBJECT	EXPER. PERIOD	NO. OF OBSERVATIONS	BLOOD VOL.	PLASMA VOL.	'AVAILABLE FLUID' VOL.	HEMATOCRIT	PLASMA PROTEIN
			Cc/kg. body weight			% red cells	Gm/100 cc.
E	Condit.	3	79.73 $\pm$ 3.29	47.97 $\pm$ 1.83	209.7 $\pm$ 7.8	43.4 $\pm$ 0.74	6.2 $\pm$ 0.12
	Heat	6 <sup>1</sup>	82.18 $\pm$ 3.58	50.58 $\pm$ 2.65	220.4 $\pm$ 14.0	42.3 $\pm$ 1.87	6.1 $\pm$ 0.10
	Cold	5 <sup>1</sup>	80.28 $\pm$ 5.27	48.10 $\pm$ 3.50	210.6 $\pm$ 24.6	44.4 $\pm$ 1.28	6.4 $\pm$ 0.18
	Reheat	2	80.40 $\pm$ 1.69	49.95 $\pm$ 0.64	201.7 $\pm$ 3.7	41.8 $\pm$ 0.64	6.1 $\pm$ 0.10
H	Condit.	3	80.80 $\pm$ 5.56	48.57 $\pm$ 2.21	239.4 $\pm$ 9.0	44.1 $\pm$ 0.90	6.2 $\pm$ 0.07
	Heat	6 <sup>1</sup>	82.25 $\pm$ 6.19	51.47 $\pm$ 4.71	232.0 $\pm$ 8.6	41.2 $\pm$ 1.51	6.1 $\pm$ 0.12
	Cold	5 <sup>1</sup>	81.88 $\pm$ 1.91	48.44 $\pm$ 0.66	231.7 $\pm$ 18.3	45.6 $\pm$ 0.60	6.6 $\pm$ 0.06
	Reheat	1	80.50	49.40	216.3	42.6	6.3
P	Condit.	3	78.43 $\pm$ 3.11	47.13 $\pm$ 2.30	243.1 $\pm$ 12.2	43.7 $\pm$ 0.95	7.0 $\pm$ 0.44
	Heat	6 <sup>1</sup>	81.25 $\pm$ 5.91	47.43 $\pm$ 4.85	222.6 $\pm$ 6.2	42.3 $\pm$ 1.64	6.2 $\pm$ 0.13
	Cold	5 <sup>1</sup>	82.10 $\pm$ 3.10	50.06 $\pm$ 2.00	216.8 $\pm$ 16.5	43.0 $\pm$ 0.45	6.2 $\pm$ 0.06
	Reheat	2	78.80 $\pm$ 3.38	49.55 $\pm$ 2.90	222.2 $\pm$ 29.3	41.1 $\pm$ 0.95	6.0 $\pm$ 0.10

<sup>1</sup> Mean plasma protein values are based upon one less observation.

Regarding acclimatization to cold, it has been demonstrated in these studies that vasoconstriction occurs more rapidly and completely in test subjects, with successive exposures to cold. This evidence was obtained through analysis of the time each man could sit quietly in the cold before reaching the arbitrarily established toe and knee temperatures necessary for commencing a period of exercise. Although these data are statistically significant in two of the three test subjects, the investigators strongly believe that such phenomena do not represent acclimatization to cold since there is no indication that they improve man's tolerance to cold.

The methods used for measuring water balance do not take into account the water content of the food, the water produced during metabolism, insensible

water loss, or fecal water content, nor were urinary solids measured. However, a consistently higher output of urine during the entire period of cold exposures produced a negative water and electrolyte balance in all of the test subjects. These phenomena persisted to some degree during the five-day period of re-exposure to heat in *subjects E and H*, and were noted in *subject P* during the first two days of this period. The mechanism of decreased water retention during cold apparently is not readily reversible. Diuresis during the period of initial exposure to cold has been recorded previously (10), but no evidence has been presented prior to this study that, with intermittent exposures to cold stress, diuresis and negative chloride balance may persist for a longer period. It is possible that these results are due to previously-stored body water and salt accumulated during the initial period of heat exposures or to partial re-accumulation during weekends so that upon exposure to cold the diuresis effect is more marked than if the test subjects had been subjected to cold without prior heat acclimatization.

The studies of body water, assessed by measurements of plasma and 'available fluid' (thiocyanate space) volumes reveal no significant changes in the partition of body water during any of the exposure periods. In general, these observations tend to confirm previous studies (7). The plasma proteins and hematocrits, however, show a definite trend toward hemodilution in the heat and hemoconcentration in the cold, similar to findings of Adolph and Molnar (10). Conley and Nickerson (27) found a decrease in thiocyanate space in two of four experiments in transferring subjects from heat to cold, but this change was not statistically significant. Forbes *et al.* (28) found an average decrease in thiocyanate space of 11 per cent in a group of 10 individuals transferred from Massachusetts to Mississippi, but the degree of variation among individuals was too great to permit much significance to be attached to their results. In the present studies, there was a slight decrease in body weight in all subjects during the period of cold exposure, compared to the first heat exposure. Spealman *et al.* (18) have presented similar but not conclusive evidence for loss of water during cold and retention during heat.

#### SUMMARY

Three healthy, unacclimatized, white males were intermittently exposed successively to a preliminary two-week period of physical conditioning, to 19, 5 $\frac{1}{4}$ -hour periods of heat (107°F. D.B.; 98°F. W.B.; wind 3 m.p.h.); 14, 5-hour periods of cold (-20°F.; wind 3 to 4 m.p.h.); 5 re-exposures to heat; a 5-week interval of no exposures to environmental stress; and finally 3 re-exposures to heat.

Through the entire experimental periods, measurements were made of cardiovascular and metabolic functions, water and chloride balance and body water partition. The results of these studies reveal that: *a*) in heat-acclima-

tized men, no acceleration of de-acclimatization is caused by repeated intermittent exposures to cold; b) acclimatization to heat may be maintained for periods of several months by occasional re-exposure to the original environmental stress; c) toe temperatures during repeated cold exposures decreased more rapidly with successive exposures suggesting more rapid and complete vasoconstriction, which does not necessarily represent acclimatization to cold since no increased tolerance to cold was demonstrated; d) marked diuresis and negative chloride balance were observed throughout the entire period of cold exposures and these phenomena tended to persist during subsequent re-exposures to heat; and e) no significant differences in total blood, plasma or 'available fluid' (thiocyanate space) volumes were found in any of the experimental periods although the plasma proteins and hematocrit values suggested *hemodilution in heat and hemoconcentration in cold*.

The relationship of these findings to problems of cold acclimatization and cross-acclimatization are discussed.

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# *Orthostatic Hypotension Following Hot or Cold Baths<sup>1</sup>*

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**T**HERMAL AGENTS are highly regarded as therapeutic measures in medicine. As a consequence, in their free employment for beneficial effects, their potentialities for injury are all too frequently ignored. Heat, regardless of whether it is used in its positive aspect, as in a hot bath, or in its negative aspect, as in a cold bath, is a means of placing the organism under stress. One need only consider the influences of hot and cold climates on man to appreciate this stress factor. In general the severity of the stress placed on an organism by any given procedure is dependent to a large extent upon the intensity of the stimulus. Thus if the stimulus is relatively mild, the organism can make adequate adjustments to maintain the constancy of its milieu interieur. In such situations the extent of these compensatory adjustments, and thus the degree of stress, can be more completely evaluated by subjecting the individual to an additional stress producing stimulus. This principle has been employed in the experiments to be reported in which a standard stress situation, viz. change in posture, has been superimposed upon the initial stimulus of temperature—a hot or a cold bath.

## PROCEDURE

Twenty-two subjects were employed, 9 males and 13 females. Their average age was 28 years (range 21-46), average height, 165 centimeters (153-178), weight, 66 kg. (55-82) and surface area 1.70 square meters (1.49-1.94). All were in excellent physical condition.

After a preliminary rest period of one-half hour at an ambient temperature of 25° to 27°C., observations were made on the subjects in the supine and erect (70°) positions. Position was changed by means of a tilting ballistocardiograph at five-minute intervals except when syncope shortened the time in the erect position. In the erect position the weight was supported by the legs. No attempt was made to diminish postural sway or movement, other than admonitions to stand still. The heart rate (by palpation or auscultation) and the blood pressure (Riva Rocci method) were determined simultaneously at one-minute intervals in each position. Ballistocardiograms were made during the last minute in each supine position and the first minute of each erect position. If syncope developed, additional cardiac output readings were obtained, but in the majority of these cases the slight involuntary movements of the subjects interfered with accurate recording.

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Two sets of postural changes were made in the control period. The subject was then immersed to the neck for 20 minutes in a tank containing 450 gallons of water maintained at a temperature of either  $18^{\circ}$  or  $40^{\circ} \pm 0.2^{\circ}\text{C}$ . Heart rates were obtained every minute and blood pressure every two minutes during the immersion. At the completion of the bath, the subject was returned to the ballistocardiograph and observed through two supine and two erect periods in the same manner as in the control periods. An additional cardiac output reading was secured in the first minute of the supine position after removal from the bath. Stroke volume and cardiac output were calculated from the ballistocardiogram employing Starr's area formula (12). Supine control values on these subjects were all within the normal limits delineated by Starr and his co-workers (12).

## RESULTS

The results of these experiments will be reported in terms of the development of orthostatic hypotension and changes in cardiac output.

*Orthostatic Hypotension.* Responses to sudden changes in position from the horizontal to the vertical have been divided into three groups: syncopal, abnormal and normal (3). The syncopal group includes those subjects who developed syncope and were unable to remain erect for five minutes. When upright these subjects developed some or all of the typical symptoms and signs of syncope, in varying intensity. Apprehensiveness, increasing discomfort, nausea, lightheadedness, dizziness and a sensation of impending collapse were almost invariably present. These symptoms were accompanied by various signs—yawning, deep breathing, increasing pallor, a steadily falling blood pressure with a low pulse pressure and a rapid, weak pulse. In some subjects, just before syncope, the heart slowed markedly. All signs and symptoms quickly disappeared on return to the horizontal position.

The abnormal group includes those subjects who remained erect for the required time but who during at least one of the erect periods sustained a fall in systolic blood pressure to abnormally low levels here defined as 100 mm. Hg or less, provided that the level was at least 10 mm. Hg lower than the lowest control, erect systolic blood pressure. Some of these subjects developed symptoms and signs similar to those in the syncopal group.

The normal group includes all of the other individuals who remained erect after the bath without symptoms and with systolic blood pressures above 100 mm. Hg.

*Hot Bath.* In the control period prior to immersion in the hot bath, there were 19 normal, 3 abnormal and 0 syncopal responses. The 3 abnormal responses were so grouped because of their blood pressure changes; no subject developed the usual signs and symptoms of syncope. Therefore, this grouping was of only borderline significance. Following immersion for a 20-minute period in water at  $40^{\circ}\text{C}$ . there were 10 normal, 8 abnormal and 4 syncopal responses. Table 1 indicates the progressive fall in blood pressure from the normal through the abnormal to the syncopal groups. The values for the heart

rate were not so consistent although the syncopal group had the lowest levels. Syncope was most closely related to systolic blood pressure and was most likely to occur when this reached the mid-eighties. Circulatory failure in the erect position was more marked in the second erect period although it did occur in

TABLE 1. CARDIOVASCULAR RESPONSES TO CHANGE IN POSTURE BEFORE AND AFTER HOT AND COLD BATHS (ALL VALUES ARE THE AVERAGES OF THE FINAL READINGS FOR EACH PERIOD)

	COLD BATH (18°C.) SUBJECTS		HOT BATH (40°C.) SUBJECTS		
	9 Normal	2 Abnormal	19 Normal	3 Abnormal	
Supine <i>before</i> <sup>1</sup> bath					
Syst. & diast. press.....	120/78	118/82	116/70	110/72	
Pulse press.....	42	36	46	38	
Heart rate/min.....	74	72	73	74	
Erect (70°) <i>before</i> <sup>1</sup> bath					
Syst. & diast. press.....	114/83	100/80	116/76	94/70	
Pulse press.....	31	20	40	24	
Heart rate/min.....	88	76	92	88	
	10 Normal	1 Abnormal	10 Normal	8 Abnormal	4 Syncopal
Supine <i>after</i> bath					
Syst. & diast. press.....	125/83	116/84	120/66	114/63	112/58
Pulse press.....	42	32	54	49	54
Heart rate/min.....	74	68	94	94	90
Erect (70°) <i>after</i> bath					
Syst. & diast. press.....	118/85	98/80	115/79	100/67	98/64
Pulse press.....	33	15	36	33	34
Heart rate/min.....	80	70	106	104	100
Supine <i>after</i> bath					
Syst. & diast. press.....	124/82	110/80	113/70	110/65	112/60
Pulse press.....	42	30	43	45	42
Heart rate/min.....	68	70	82	79	75
Erect (70°) <i>after</i> bath					
Syst. & diast. press.....	116/83	100/80	112/80	95/72	90/72
Pulse press.....	33	20	32	23	18
Heart rate/min.....	78	76	96	108	92

<sup>1</sup> These figures are from the second control periods.

both. This is indicated not by a greater number of syncopal attacks or abnormal responses but by the greater fall in blood pressure in the second erect period.

Figure 1 indicates the response of a subject in the normal group while figures 2 and 3 are typical of abnormal and syncopal responses respectively. In figure 3 syncope was delayed until the second period. In this subject, the first erect period was tolerated without difficulty but with somewhat reduced blood

pressure and heart rate. The presence of the bradycardia might be considered significant, since some of the symptoms of syncope were present despite the fact

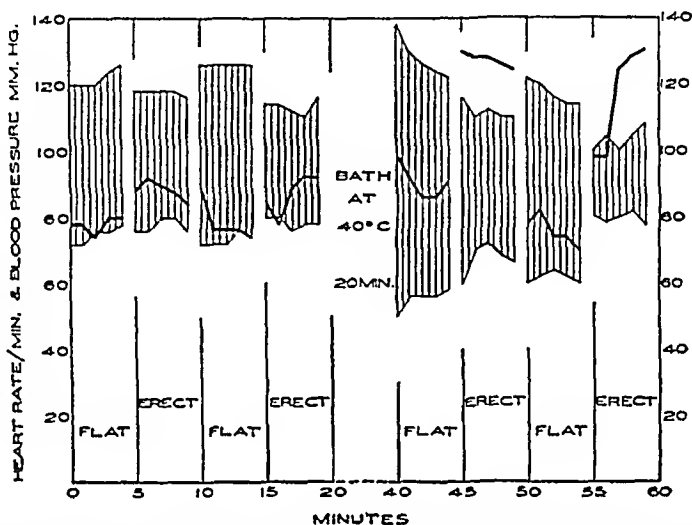


Fig. 1. A NORMAL BLOOD PRESSURE response to erect posture following a hot bath. The heavy black line indicates the heart rate: the upper level of the striped area, the systolic blood pressure; the lower level, the diastolic blood pressure.

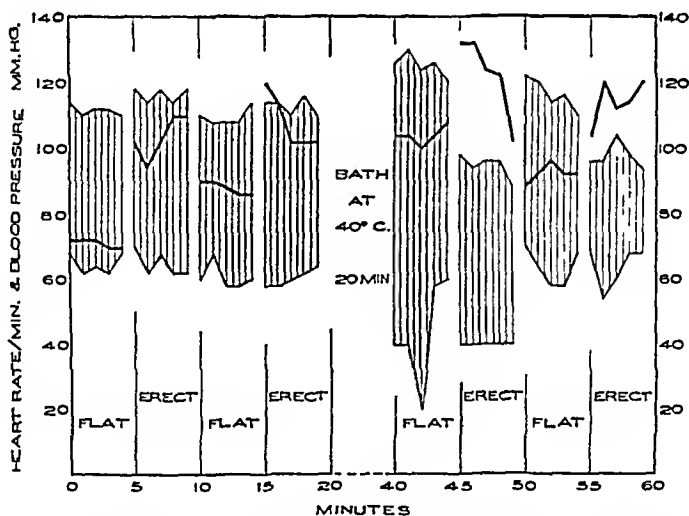


Fig. 2. AN ABNORMAL BLOOD PRESSURE RESPONSE following a hot bath. See fig. 1 for explanation.

that there was no great fall in blood pressure. Signs of syncope were evident early in the second period and progressed rapidly to the point where neither blood pressure nor heart rate was obtainable.

Repetition at a later date of this thermal stress on 3 subjects—one from each group—gave doubtful evidence of any tendency for improvement in the 2

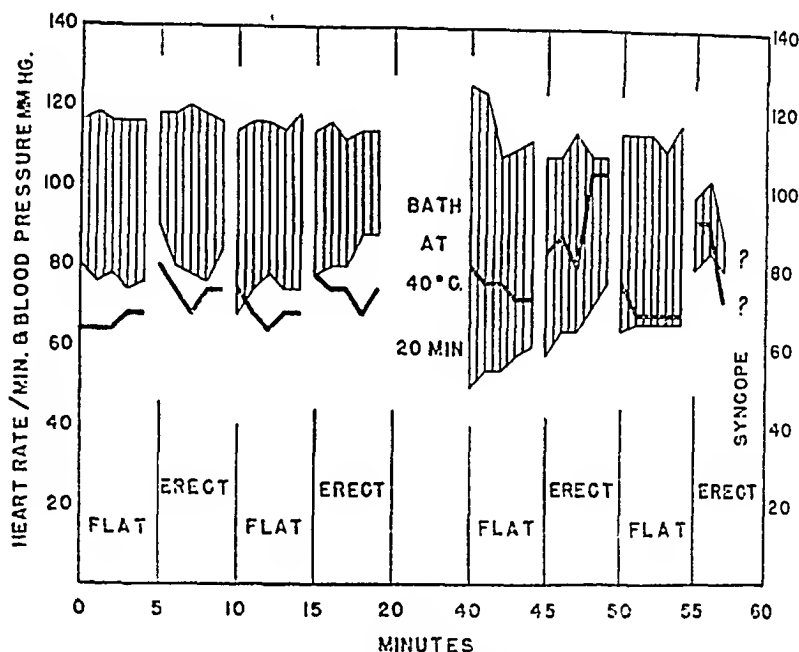


Fig. 3. ORTHOSTATIC HYPOTENSION WITH SYNCOPE following a hot bath. See fig. 1 for explanation.

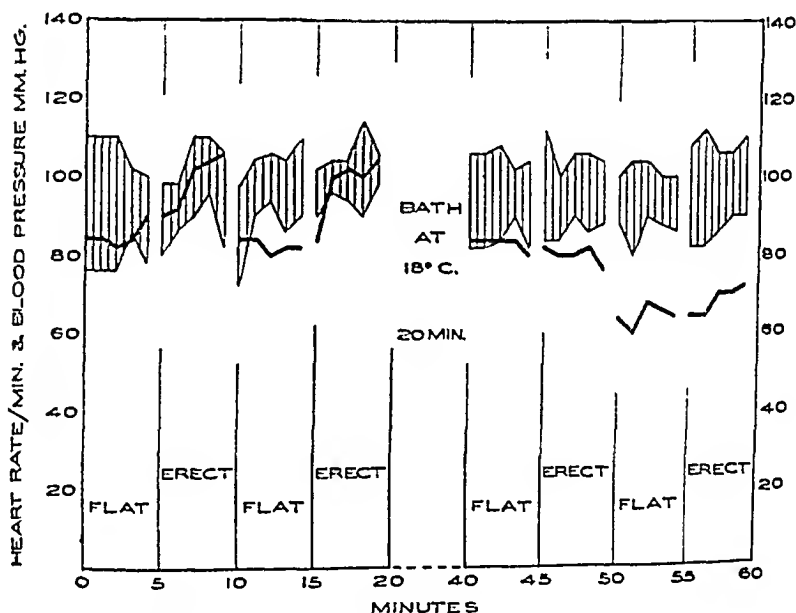


Fig. 4. A NORMAL BLOOD PRESSURE RESPONSE to erect posture following a cold bath. See fig. 1 for explanation.

abnormal subjects. The individual who had a syncopal response on the first test had another syncopal followed by another abnormal response. In the normal subject a repeat test again resulted in a normal type of response.

*Cold Bath.* In the control period prior to immersion in water at 18°C. there were 9 normal, 2 abnormal and 0 syncopal responses. The 2 abnormal responses occurred in 2 of the same individuals who showed abnormal responses in the control period prior to the hot bath. Following immersion in the cold bath there were 10 normal, 1 abnormal and 0 syncopal responses. Thus following the cold bath the abnormal pattern remained in one individual while in the other individual the abnormal response was converted to an essentially normal response. The normal type of response following the cold baths differed from the pre-bath or control tilts only in the fact that the erect posture was now maintained with only minor increases in heart rate, (fig. 4 and table 1).

*Cardiac Output.* All results are presented as percentage deviations from control values, since most of the uncertainties of the ballistocardiographic method disappear when it is used to assess changes occurring in the same individual. Analyses of the ballistocardiographic data in these experiments have been made in two ways. Table 2 presents the data in such a manner as to evaluate the double stress of bath and change in posture. The values of the control supine positions were used as base figures. Table 3, on the other hand, presents the data from the standpoint of evaluating the change in posture alone regardless of any other stress. The percentile differences were calculated from values obtained during a supine position immediately prior to the assumption of each erect position.

*Hot Bath.* The data as presented in tables 2 and 3 have been separated into two broad classifications dependent upon the blood pressure changes and subjective sensations observed on the passive assumption of the erect position. The abnormal response group included those who developed frank syncope as well as those who showed minor indications of impending collapse. The very definition of abnormal response makes this grouping rather complex and accounts for the generally wider variability observed in this group.

There was no significant difference in the control observations made on these two groups. The abnormal group as a whole tended to have higher heart rates following the sudden shift of position (table 2 and fig. 5). The post-bath tilts were accompanied by large cardiac outputs, a consequence of increases in both stroke volume and heart rate. The abnormal group had a significantly higher cardiac output during the first stand five minutes after immersion—an indication of the greater stress. Figure 5 illustrates these changes. The normal *subject H* and the abnormal *subject W* were selected for presentation primarily because their responses in the control tilts were not typical of their respective groups and so demonstrated the inadvisability of predicting post-bath responses on the basis of control observations.

The inability of the abnormal group to meet the strain of the additional stress imposed by the passive shift in position is shown by the data of tables 1 and 3. The vasodilation induced by the hot bath placed the cardiovascular

TABLE 2. PERCENTAGE DEVIATIONS FROM BASAL VALUES OF CARDIOVASCULAR RESPONSES WITH POSTURAL CHANGES BEFORE AND AFTER HOT AND COLD BATHS

TIME OF OBSERVATION	CARDIAC OUTPUT			STROKE VOLUME			HEART RATE		
	Mean Control Value cc/lb/min.	% Change		Mean Control Value cc/beat	% Change		Mean Control Value/ min.	% Change	
		Mean	S.E. <sup>2</sup>		Mean	S.E.		Mean	S.E.
Cold bath 18°C.....	26.4			55.4			72		
Before.....		-7	3.4		-22	2.8		21	2.1
5 min. after <sup>1</sup> .....		-16	2.6		-20	3.6		10	2.9
15 min. after <sup>1</sup> .....		-14	1.1		-17	2.9		5	1.0
Hot bath 40°C.....									
Normal resp.....	25.7			54.5			70		
Before.....		-2	5.0		-20	3.2		22	5.2
5 min. after <sup>1</sup> ....		54	13.3		-8	7.5		66	12.6
15 min. after <sup>1</sup> .....		26	9.9		-15	4.7		44	7.0
Hot bath 40°C.....									
Abnormal resp.....	25.7			50.5			71		
Before.....		8	5.6		-18	3.0		35	5.3
5 min. after <sup>1</sup> .....		65	7.8		-4	4.2		62	8.1
15 min. after <sup>1</sup> .....		29	3.4		-16	4.0		44	6.5

<sup>1</sup> Subject was passively tilted to erect (70°) posture at this time and observations were recorded during the first 45 sec. of the erect position. <sup>2</sup> Standard error of mean.

TABLE 3. PERCENTAGE DEVIATIONS IN CARDIOVASCULAR RESPONSES TO A CHANGE IN POSTURE (FROM DATA OBTAINED ONE MIN. BEFORE AND WITHIN ONE MIN. AFTER EACH TILT TO ERECT POSITION)

TIME OF OBSERVATION	CARDIAC OUTPUT % CHANGE		STROKE VOLUME % CHANGE		HEART RATE % CHANGE	
	Mean	S.E.	Mean	S.E.	Mean	S.E.
Cold Bath 18°C.						
Before.....	-7	3.4	-22	2.8	21	2.1
5 min. after <sup>1</sup> .....	-16	3.8	-21	2.4	8	3.8
15 min. after <sup>1</sup> .....	-7	1.5	-17	2.2	15	5.5
Hot Bath 40°C.						
(Normal resp.)						
Before.....	-2	5.0	-20	3.2	22	5.2
5 min. after <sup>1</sup> .....	29	9.9	-7	7.3	13	6.8
15 min. after <sup>1</sup> .....	14	5.7	-9	5.0	21	5.9
(Abnormal resp.)						
Before.....	8	5.6	-18	3.0	35	5.3
5 min. after <sup>1</sup> .....	2	7.9	-20	6.4	18	3.1
15 min. after <sup>1</sup> .....	7	3.8	-16	3.4	36	5.3

<sup>1</sup> Subject was passively tilted to erect (70°) posture at this time and observations were recorded during the first 45 sec. of the erect position.

system under considerable tension. When these individuals were subjected to the erect posture neither the stroke volume nor the heart rate was able to meet the situation. Consequently, the cardiac output failed to rise to adequate levels and syncopal symptoms developed. More adequate responses were present 10 minutes later.

**Cold Bath.** Average cardiac output was decreased slightly during the erect position prior to immersion in cold water. This change was effected primarily by a lowering of the stroke volume, compensated to some extent by an increased heart rate. Following the bath the erect posture was tolerated much more efficiently (table 1). The heart rate was significantly depressed in rela-

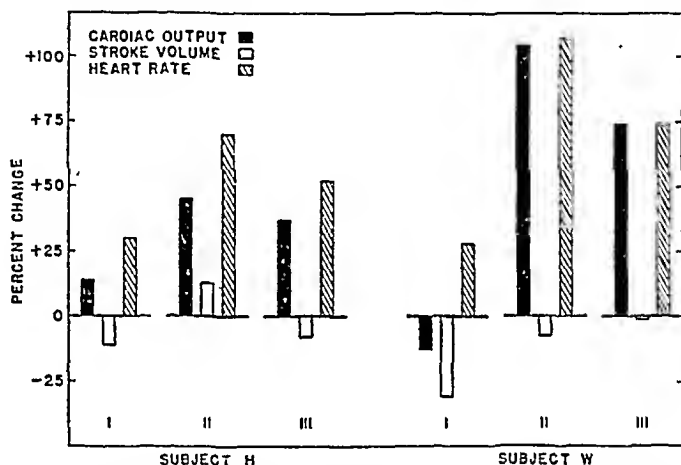


Fig. 5. PERCENTILE CHANGES from basal supine levels in cardiac output, stroke vol. and heart rate of 2 subjects. Values were obtained during the first min. of a 70° erect position: I, Prior to a cold bath; II, 5 min. after the bath; III, 10 min. after the bath. Subject H had a normal response to the postural changes, while subject W's response was abnormal.

tion to the values obtained in the control tilts and since the stroke volume remained constant, cardiac output was lowered even more (tables 2 and 3).

#### DISCUSSION

The development of orthostatic hypotension is probably related to an inadequate return of the blood to the heart. How much of a decrease in the cardiac output is necessary before syncope develops is not known. Grollman (5) reported cardiac output to be unchanged in the erect posture while McMichael (8), Scott (10), and Asmussen and Knudsen (1) have found outputs decreased as much as 20 per cent. When cardiac output was measured by the technique of right atrial catheterization, a 15 to 45 per cent decrease in the erect posture was observed by several investigators (10, 13, 14). No consistent changes in cardiac output (ballistocardiograph) in subjects in the recumbent or relaxed erect posture were noted by Starr and Rawson (11). In all probability



this discrepancy is related not to differences in technique but to the relative stage of development or lack of development of orthostatic hypotension. The results obtained on the present group of subjects agree well with the data presented by Starr and Rawson (11). There was a mean change of plus one per cent in cardiac output, a 20 per cent decrease in stroke volume and a 27 per cent increase in heart rate when the erect posture was passively assumed. Of the 33 tests in which duplicate records were obtained, cardiac output was decreased in 23 and increased in 10 instances.

Following the hot bath it was possible to separate the subjects into two groups, viz. normal and abnormal reactors. Re-evaluation of the data obtained in pre-bath stands showed some interesting tendencies, i.e. that the group having a normal response was able to stand effectively with a reduced cardiac output while those who under additional stress might go into syncope responded by increasing the cardiac output. When the stress became greater the members of the latter group were unable to meet the demands made on their cardiovascular system and so developed syncopal tendencies. The importance of the stress factors in evaluating physiological responses is indicated also by the inability to predict syncope from the data obtained from the supine subject after the hot bath. There was no great disparity in the blood pressure, heart rates and cardiac output of the three groups at this time, indicating that the circulatory disturbance was revealed only under additional stress, i.e. the erect position.

Orthostatic hypotension developed in approximately 50 per cent of individual cases following a 20-minute immersion in a bath with a temperature of 40°C. Eichna, Horvath and Bean (3) and Mayerson (7) observed a somewhat similar percentage of hypotensive responses with or without syncope in individuals following periods of acute exhausting or prolonged enduring work. Furthermore, Eichna and Horvath (2) have observed that on the first day of moderate work (approximately 250 Cal/hr.) in hot environments such as those found in normal deserts and severe tropics, approximately one half of the men so exposed have a tendency to develop postural hypotension when assuming an erect posture immediately upon the completion of work. In one half of the subjects with postural hypotension, fall in blood pressure was so severe as to produce syncope.

In all of these situations two physiological phenomena have existed, viz., elevated body temperature and varying degrees of peripheral vasodilation. An additional factor that was common to several of these situations was the presence of varying degrees of hyperventilation. Engel *et al.* (4) have noted that in individuals with postural maladaptation, hyperventilation accelerated the fall in blood pressure upon assumption of the erect posture. In all individuals following hot baths there was an increased respiratory exchange (6), although

the hyperventilation was not so marked as in the studies reported by Engel *et al.* (4). It is conceivable that the additional peripheral vasodilation as a consequence of hyperventilation was sufficient in conjunction with the other peripheral effects due to heat alone to disturb the fine balance present and induce syncope tendencies in the abnormal group.

The generalized vasodilation induced by heat probably produced a decreased blood volume due to loss of fluid into tissue spaces. Additional pooling of both blood and tissue fluid in the dependent extremities, as a consequence of capillary dilation and delayed emptying of veins, would reduce still more the amount of blood that could be returned to the heart. Therefore, it would seem that the failure of the pressor sensible reflexes and the pooling of fluid and blood resulted in diminished cardiac output and induced orthostatic hypotension.

Both vasoconstriction and pulse acceleration are carried out by the same mechanism—vasomotor sympathetic reflexes. These reflexes were not brought into effective action in those individuals who developed orthostatic hypotension following the hot bath. It would appear that the failure was two-fold, viz., not only a failure to initiate adequate stimuli but also, probably more importantly, an inability to provide adequate stimuli to overcome the direct effects of heat. The heart rate did not increase in the abnormal reactors in contrast to the relatively large acceleration in the normal individuals. Although vasoconstriction probably occurred to some extent in the erect position it was not possible to demonstrate the effect. Regardless of the extent of this reflex response, it was not effective in shifting blood to the required tissues.

It would appear that orthostatic hypotension developed primarily as a consequence of failure to provide an adequate return of blood to the heart. In the present series the stroke volume was reduced (table 3) following passive tilting to the erect position even when the cardiac output had been increased due to the stress of a hot bath. The acceleration of heart rate was inadequate to compensate for the degree of stress involved.

The marked ease with which all individuals were able to tolerate the erect posture following the cold bath, despite reduced cardiac output, illustrated the importance of pressor (local or central) stimuli. Constriction of blood vessels is the basis of the compensatory mobilization of blood from other regions helping to maintain the return of blood in the erect posture. Due to the presence of vasoconstriction the arterial bed readily adapted itself to the diminished cardiac output. The vasoconstrictor effect was so powerful that cardiac acceleration was not called into action to increase cardiac output. The vasoconstriction and possibly also the improved venous return resulting from the increased muscular tone induced by the cold exposure enabled individuals to stand (70°) with reduced demands on the cardiovascular system.

## SUMMARY

Passive alteration of posture from the supine to the erect ( $70^{\circ}$ ) was accompanied by an elevated heart rate and a reduced stroke volume. The cardiac output was increased slightly in those individuals who later developed abnormal responses to the change in posture following heat stress but was lowered in those who were able to tolerate the shift without difficulty. Approximately one half of the subjects developed orthostatic hypotension following immersion in a hot bath ( $40^{\circ}\text{C}.$ ) for 20 minutes. The causative factor appears to be the result of a combination of pooling of blood and fluid in the dependent extremities and a failure of the pressor-sensible reflexes to induce steps that would bring forth the requisite increase in cardiac output. The erect posture was maintained with greater ease and reduced cardiovascular demands following a cold bath ( $18^{\circ}\text{C}.$ ).

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# Effects of Acute Hypoxia on Renal Circulation in Man<sup>1</sup>

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THE ACUTE EFFECTS on para-amino hippurate (PAH) and inulin clearances, plasma glucose levels and arterial blood pressure of breathing low oxygen mixtures at atmospheric pressure have been followed in 10 experiments on 2 normal males aged 23 and 28 years. The administration and determination of PAH and inulin for the clearances was as previously described (1). The subjects were recumbent for 30 minutes or more before clearance periods began and remained so throughout all periods. After two control periods on room air, the subject during the third period inspired from a 150 liter Tissot spirometer, expiring to outside air; after the period on the spirometer two more periods were followed on room air. Blood pressure was determined frequently through all periods by the auscultatory method. In one experiment on each subject room air was breathed from the spirometer during the third period to determine whether the spirometer breathing alone affected clearances or blood pressure. In the other experiments mixtures of room air and nitrogen were in the spirometer, the lowest oxygen percentage employed being 9.3, or 69.6 mm. Hg oxygen tension. Oxygen determinations of spirometer mixtures were determined by a Beckman oxygen analyzer or by Scholander's technique (2) or by both. The blood pressures shown in the tables are the averages of the values obtained during the respective periods; mean pressure is given as diastolic plus 40 per cent of pulse pressure. Renal vascular resistance units per square meter ( $RRU/M^2$ ) are expressed as: mean arterial pressure (mm. Hg) minus 5/renal blood flow in cc/sec/ $M^2$ , renal blood flow being taken as  $PAH \text{ clearance}/1 - H_c$ , where  $H_c$  is hematocrit cell percentage volume. Filtration fraction (FF) is inulin clearance/PAH clearance. The results are seen in tables 1 and 2.

## RESULTS

*Subject SOL* has been an army pilot and was accustomed to exposures to low oxygen tensions; he was not at all apprehensive and showed little or no increase in respiratory minute volume on the low oxygen mixtures. *Subject FTC*, even though he had breathed 10 or 12 per cent oxygen on several occasions before the clearance experiments were done in order to become accustomed to the

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procedure, was still somewhat apprehensive in the first two low oxygen experiments (6/23/48 and 7/1/48); he showed much greater increases in respiratory

TABLE I. EFFECT OF HYPOXIA ON RENAL CIRCULATION IN F. T. C.

DATE	PAR CLEARANCE	INULIN CLEARANCE	F. F.	PLASMA GLUCOSE	BLOOD PRESSURE			RRU/ $M^2$
					Syst.	Diast.	Mean	
	cc/min/ $M^2$	cc/min/ $M^2$		mg. %	mm. Hg	mm. Hg	mm. Hg	
6/15/48	During 16½ of the 18 min. of 3rd period subject breathed room air from a spirometer							
	299	69	0.23	104	131	66	92	9.9
	326	73	0.22	93	125	69	92	9.1
	291	69	0.24	102	127	68	92	10.2
	302	72	0.24	104	123	67	89	9.5
	270	66	0.24	94	122	69	90	10.7
6/23/48	During 5¼ of the 7½ min. of 3rd period subject breathed 11.7% O <sub>2</sub> from spirometer							
	336	54	0.16	91	123	69	91	8.7
	330	59	0.18	99	122	67	89	8.7
	216	62	0.29	97	140	68	97	14.5
	314	57	0.18	99	124	66	89	9.1
	303	60	0.20	93	119	67	88	9.3
7/ 1/48	During 7½ of the 9 min. of 3rd period subject breathed 10.7% O <sub>2</sub> from spirometer							
	349	67	0.19	102	122	68	90	8.3
	299	60	0.21	98	124	68	90	9.7
	259	52	0.20	81	141	66	96	11.9
	317	59	0.19	94	122	67	89	9.0
	258	55	0.21	98	117	65	86	10.6
7/13/48	During 4½ of the 5¾ min. of 3rd period subject breathed 9.4% O <sub>2</sub> from spirometer							
	290	73	0.25	109	124	64	88	9.8
	309	74	0.24	103	124	63	87	9.0
	291	73	0.25	106	148	37	81	8.9
	318	71	0.22	108	123	61	86	8.7
	289	70	0.24	115	121	62	86	9.5
7/21/48	During 6½ of the 8 min. of 3rd period subject breathed 13% O <sub>2</sub> from spirometer							
	287	55	0.19	106	117	66	86	9.6
	324	61	0.19	102	119	66	87	8.6
	307	63	0.20	96	135	65	93	9.8
	305	57	0.19	103	117	64	85	8.9
	305	56	0.18	100	117	64	85	8.9
8/4/48	During 15¼ of 16¾ min. of 3rd period subject breathed 10.5% O <sub>2</sub> from spirometer							
	334	67	0.20	103	127	65	90	8.9
	291	61	0.21	106	128	66	91	10.0
	330	65	0.20	101	143	63	95	9.3
	321	65	0.20	101	123	63	87	8.7
	310	64	0.21	102	122	66	88	9.1

minute volume than did SOL. It is believed that the clearance falls seen in these two experiments are the results of renal vasoconstriction of psychic origin;

the subsequent experiments on *FTC* and all on *SOL* showed no consistent changes in clearances during or after breathing low oxygen. In no case did protein or glucose appear in the urine. The fall in PAH clearance in *FTC* on June 23, 1948 was greater than on July 1, 1948 and was the only instance with either subject where a striking rise in filtration fraction occurred, but even in this period there was no rise in plasma glucose indicative of adrenalin output during the low oxygen period.

TABLE 2. EFFECT OF HYPOXIA ON RENAL CIRCULATION IN S. O. L.

DATE	PAH CLEARANCE	INULIN CLEARANCE	F. F.	PLASMA GLUCOSE	BLOOD PRESSURE			RRU/M <sup>2</sup>
					Syst.	Diast.	Mean	
	cc/min/M <sup>2</sup>	cc/min/M <sup>2</sup>		mg. %	mm. Hg	mm. Hg	mm. Hg	
7/17/48	During 6 of the 7½ min. of 3rd period subject breathed room air from spirometer							
	353	59	0.17	108	115	71	89	7.7
	344	48	0.14	108	116	71	89	7.9
	311	48	0.15	103	120	69	89	8.7
	308	42	0.14	103	117	73	91	9.0
	296	50	0.17	109	119	72	91	9.4
7/24/48	During 17½ of the 19 min. of 3rd period subject breathed 10% O <sub>2</sub> from spirometer							
	365	75	0.20	101	119	71	90	7.6
	335	68	0.20	100	118	72	90	8.2
	342	78	0.23	110	124	77	96	8.6
	305	58	0.19	103	121	72	92	9.2
	292	60	0.20	107	119	74	92	9.6
7/31/48	During 14½ of the 16½ min. of 3rd period subject breathed 13% O <sub>2</sub> from spirometer							
	339	63	0.19	94	116	74	91	8.2
	305	59	0.19	95	117	74	91	9.1
	351	66	0.19	103	120	72	91	7.9
	306	68	0.22	105	117	68	88	8.8
	262	63	0.24	97	117	74	91	9.6
10/10/48	During 12½ of the 14½ min. of 3rd period subject breathed 9.3% O <sub>2</sub> from spirometer							
	342	73	0.21	98	120	71	91	8.2
	342	70	0.21	94	120	69	89	8.0
	390	72	0.18	88	125	62	87	6.8
	333	70	0.21	93	121	68	89	8.2
	319	71	0.22	85	118	69	89	8.5

The blood pressure responses are not fully shown in the tables, which give only the averages of the readings in each period. Subject *SOL* showed only slight changes, the systolic usually rising a few mm. on low oxygen with the diastolic showing a slight rise or fall or no change, resulting in slight or no change in mean pressure. The responses of *FTC* were considerably greater, there being always a considerable rise in systolic, no change or a slight fall and on one occasion (7/13/48) a large fall in diastolic, with a resultant slight rise in mean, except for a fall on July 13, 1948.

In the absence of changes in PAH clearance there is no change in renal vascular resistance; on the two occasions where PAH clearance fell (*FTC*, 6/23/48 and 7/1/48) there is a slight rise in renal resistance, ascribable to psychic effect rather than to the hypoxia. There is a suggestion that, in the absence of psychic effects, *SOL* in his last two experiments showed a slight fall in renal resistance but the falls are only slightly beyond the spontaneous fluctuation.

Since this work was completed, a paper by Kelley and McDonald (3) has appeared reporting that glomerular filtration rate in unanesthetized dogs is not consistently influenced by acute exposure to high altitude and that PAH *Tm* is sometimes increased and glucose *Tm* usually decreased; there is no statement on PAH clearances.

#### SUMMARY

Breathing of low oxygen mixtures at atmospheric pressure, the lowest being 9.3 per cent, for periods of a few minutes produced no effect on PAH or inulin plasma clearance, renal vascular resistance or plasma glucose levels in 2 normal young male adults.

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## *Effect of Mannitol on Salt Excretion during Water Diuresis*

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IN THE COURSE OF EXPERIMENTS in which mannitol was used for the determination of glomerular filtration rates (1), a study was made of the changes in water and electrolyte excretion produced during water diuresis by mannitol at blood levels usually encountered with the single injection clearance method. It was of particular interest to compare the diuretic action of mannitol under conditions of hydration with its action under conditions of dehydration.

The urine volume during hydropenia is regulated by the quantity of osmotically active substances requiring excretion, because the concentrating ability of the renal tubules is limited (2-10). It is fairly well agreed that approximately equal minimal amounts of water are required for the excretion of each osmol of glucose or electrolyte in the urine. It is not clear whether the same can be said of urea (6, 7) or whether the degree to which urea can be maximally concentrated in the presence of other solutes is unique (2, 5, 9, 10). Whatever the case, the existence of a urinary osmotic ceiling explains the fact that when the excretion of one osmotically active substance is forced under conditions of hydropenia, its urinary concentration rises, and the concentrations of other solutes fall as urine volume increases. The fact that the osmotic pressure of the urine also falls has been attributed by Hervey and McCance (8) to a reciprocal relationship between urine flow and the osmotic ceiling, and by Shannon (11) to an osmotic effect on the proximal tubular reabsorption of water which results in a sudden flooding of the mechanism of water reabsorption in the distal tubules.

The absolute rates of excretion of electrolytes may be increased during osmotic diuresis<sup>2</sup> despite the decline in their urinary concentrations. Urea (2, 12), glucose (13-16), sucrose (16-19), sorbitol (16) and mannitol (20-21), when administered in large amounts, have all been reported to increase renal loss of salt. As much as 27 per cent of the filtered chloride (14, 20, 21) can be excreted at the height of an osmotic diuresis.

As far as can be ascertained from the published data, the experiments outlined above were conducted under conditions where the exogenous supply of water was more or less limited. Crutchfield and Wood (22) observed no significant change in sodium or water excretion under conditions of water diuresis after administration of 30 gm. of urea or 75 cc. of 50 per cent glucose intravenously in human beings. They concluded that "osmotic substances tend to

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<sup>2</sup> The term 'osmotic diuresis' is used as a convenient designation for the diuresis induced by osmotically active substances, without implying any explanation of its mechanism



lose their efficiency as diuretic agents when combined with a large water intake". It is probable, however, that the amounts of urea and glucose used were inadequate to promote sufficient urinary excretion of these substances.

Gabrilove (23) pointed out that the chloruresis observed during diabetic glycosuria by Atchley and his associates (13) was complicated by water depletion, which, of itself, might have led to a secondary depletion of the body stores of salt. He was unable to demonstrate any relation between daily urinary excretion of chloride and glucose in 7 diabetic patients with glycosuria, who were allowed free access to food and water.

This paper presents data which demonstrate that mannitol and glucose may promote increased excretion of sodium and chloride during water diuresis in the absence of an increase in urine flow.

#### METHODS AND MATERIALS

Nineteen experiments of four types were performed. The subjects of the experiments in *Groups I, II* and *IV* were healthy young adult males. The subjects of the two experiments in *Group III* were adult male patients without any stigmata of renal disease.

All urine specimens were voided spontaneously without catheterization. Analyses for sodium and potassium in urine and serum were done with the flame photometer by the method of Hald (24), duplicate determinations being required to check within 2 per cent for sodium and 5 per cent for potassium. Urine chlorides were determined by a modification of the method of Volhard and Harvey (25). In the glucose experiment in *Group IV*, urinary glucose was determined by the method of Somogyi (26), and whole blood glucose by the method of Benedict (27), using zinc filtrates (28).

#### *Groups I and II*

*Experimental procedure.* A diuresis was instituted and maintained in fasting subjects by the ingestion of 250 cc. of 0.2 per cent saline or tap water per hour. Four or five hours after drinking began, the subjects assumed a semi-reclining position on a couch, and remained there for the rest of the experiment. After one hour of rest, the subjects voided and the experimental period was begun. In eight control experiments urine samples were collected at the end of each of the next two hours. In eight other experiments, one urine specimen was collected at the end of half an hour and immediately thereafter 100 cc. of 25 per cent mannitol was injected intravenously. Urine samples were then collected at the end of a second half hour and again after another hour.

*Results.* Data from two representative experiments in each group are given in table 1. The percentage changes in electrolyte excretion rates and urine flows from the first to the second collection periods are summarized in table 2. In the control experiments electrolyte excretion rates were variable,

TABLE 1. REPRESENTATIVE EXPERIMENTS FROM GROUPS I, II, AND III

SUBJECT	PERIOD	URINE SODIUM		URINE CHLORIDE		URINE POTASSIUM		URINE FLOW
		mEq/min.	mEq/l.	mEq/min.	mEq/l.	mEq/min.	mEq/l.	cc/min.
GROUP I: Controls								
1	1	.146	28.8	.109	21.5	.060	11.8	5.07
	2	.147	38.3	.093	24.2	.056	14.6	3.84
2	1	.103	20.7	.130	26.1	.048	9.6	4.98
	2	.104	18.2	.130	22.7	.047	8.2	5.72
GROUP II: Mannitol during hydration								
1	1	.185	24.3	.133	17.4	.043	5.7	7.61
	2	.300	65.5	.257	56.1	.042	9.2	4.58
	3	.291	65.8	.247	55.9	.066	14.9	4.42
3	1	.108	23.0	.118	25.0	.043	9.1	4.69
	2	.212	43.2	.217	44.5	.038	7.8	4.91
	3	.226	92.7	.226	92.1	.040	16.3	2.43
GROUP III: Mannitol during hydropenia								
4	1	.156	109	.246	171			1.44
	2	.246	70	.365	103			3.53
5	1	.078	126	.104	169			.62
	2	.140	65	.186	86			2.16

TABLE 2. PERCENTAGE CHANGES IN ELECTROLYTE EXCRETION RATES AND URINE FLOWS, FROM THE FIRST TO THE SECOND COLLECTION PERIODS

	Na	Cl	K <sup>1</sup>	H <sub>2</sub> O
Control (Group I) 8 expts.				
Mean.....	+4.1	-2.5	-18.8	-3.1
S.D.....	±18.7	±15.4	±17.6	±39.8
Mannitol (Group II) 8 expts.				
Mean.....	+47.6	+59.4	-12.0	-4.5
S.D.....	±28.4	±25.1	±8.8	±26.1
<i>t</i> .....	3.6	6.0	0.9	0.08
Probability of larger value of <i>t</i> .....	<.01	<.01	>.40	>.50

<sup>1</sup> Potassium data from 4 control experiments and from 7 mannitol experiments.

but the average changes were not significant. After the injection of mannitol there was a significant increase in sodium and chloride excretion in every instance. Urinary concentrations of these ions increased concomitantly,

whereas urine flows were either unchanged or fell off slightly. Potassium excretion declined in every instance but the average change was not significantly different from that of the control experiments.

The diuresis of sodium chloride induced by the mannitol was maintained at an essentially constant rate for at least an hour and a half following the injection.

### *Group III*

Two experiments were performed to study the effect of mannitol on salt excretion in the hydropenic state.

*Experimental procedure.* The subjects, two convalescent bed patients without any disease known to affect renal function, were fasted and thirsted for 12 hours prior to the experiment. A preliminary one-hour urine specimen was obtained and then 100 cc. of 25 per cent mannitol was injected intravenously. The second specimen consisted of all the urine voided during the next hour.

*Results.* It can be seen in table 1 that, under conditions of hydropenia, mannitol increased the urine flow and salt excretion although electrolyte concentrations in the urine declined.

### *Group IV*

The effect of a rapid glucose infusion on the salt excretion of a normal subject during water diuresis was studied in one experiment.

*Experimental procedure.* The subject, fasting, maintained a large water diuresis for six hours preceding the experiment by the ingestion of 400 cc. of tap water per hour. During the experimental period, water intake was increased to 500 cc. per hour. Two control urines were obtained over 45-minute periods. 100 cc. of 50 per cent glucose solution was then injected rapidly intravenously followed by an infusion of 500 cc. of 25 per cent glucose solution over the next 40 minutes. Urines were collected at frequent intervals for three hours after the start of the glucose infusion and analysed for glucose as well as for electrolyte content. Serial determinations of blood glucose and serum sodium were also made.

*Results.* The data, presented in table 3, show that the initial increase in sodium excretion occurs without increase in urine flow. Subsequently, urine sodium excretion rose concomitantly with, but more rapidly than, urine flow and glucose excretion. Chloride excretion rates, not recorded here, closely paralleled sodium excretion rates.

### DISCUSSION

The increase in sodium and chloride excretion in the face of constant or declining urine flows cannot be explained on the basis of a tubular osmotic ceiling (2-10) or loss of endogenous water (23). A specific effect of mannitol

is unlikely, since the same phenomenon was observed in the early stage of glucose diuresis. Intravenous mannitol may have produced temporary small increases of plasma volume. However, further large increases produced by intravenous administration of salt-poor concentrated human albumin to some of our subjects under the same conditions actually depressed the renal excretion of sodium and chloride (1). The glomerular filtration rate does not change significantly during osmotic diuresis (20, 29).

In the glucose experiment reported here, there was a transient fall in serum sodium concentration to 116 mEq/liter. Similar large falls are reported after the injection of hypertonic sugar solutions by Kerpel-Fronius (14), Wesson and Anslow (20) and Hare (15). In five experiments, not reported here, intravenous injection of 25 grams of mannitol reduced the serum sodium from 2 to 7

TABLE 3. EFFECT OF GLUCOSE ON EXCRETION OF ELECTROLYTES DURING WATER DIURESIS

PROCEDURE	PERIOD	TIME OF PERIOD	SERUM <sup>1</sup> Na	BLOOD <sup>1</sup> GLUCOSE	URINE FLOW	URINE GLUCOSE		URINE Na	
		min.	mEq/l.	mg. %	cc/min.	gm. %	gm/min.	mEq/l.	mEq/min.
Control	1	44			10.3	0	0	10.1	0.10
Control	2	46	131.0	105	9.8	0	0	9.2	0.09
Glucose <sup>2</sup> infusion	3	27			9.3	1.46	0.14	19.4	0.18
	4	28	116.3	800	18.4	2.14	0.39	24.7	0.46
Post-infusion	5	25			24.4	1.88	0.46	21.2	0.51
	6	40			13.9	2.00	0.28	27.9	0.39
	7	25	131.9	263	14.0	2.16	0.30	37.0	0.52

<sup>1</sup> Blood specimens drawn at the ends of the corresponding urine-collection periods.

<sup>2</sup> 100 cc. of 50% glucose was injected rapidly, followed by 500 cc. of 25% glucose over a period of 46 minutes.

mEq/liter. These changes probably indicate a shift of water from cells, since they are too large to be accounted for by the increased sodium excretion. It is possible that cellular dehydration, in the kidneys or elsewhere, may stimulate renal tubular rejection of salt under these conditions.

Smith and his associates (20, 21) have recently presented evidence that large mannitol infusions in dogs result in the delivery to the distal tubules of an increased volume of proximal tubular fluid which, because it remains isosmotic with plasma, contains sodium at a concentration lower than that of plasma. They hypothesize (20) that "the retention of water in the proximal urine, under the osmotic action of mannitol, may dilute the sodium concentration in the urine below that of plasma and thus establish increasing concentration gradients between urine and plasma, which progressively reduce the rate of sodium reabsorption".

Increased flow through the more distal parts of the proximal tubules, by limiting the duration of contact between tubular cells and fluid, might be another factor in proximal tubular diuresis. The fact that the overall reabsorption of phosphate and bicarbonate is practically unaffected would not necessarily militate against this possibility, since the reabsorption of these anions may be more easily adaptable to increasing loads which are smaller than the loads of sodium and chloride.

Under the hypothesis of a primarily proximal tubular action of mannitol or glucose, the fact that the urinary excretion of salt is increased in osmotic diuresis indicates that the distal tubular mechanism for salt reabsorption either reaches a maximum or is only slowly adjustable to increasing salt loads. A delayed tubular adjustment is suggested by the observation of several workers (13, 14, 18) that continuing melituria results in a decline of the initially increased level of salt excretion.

Distal tubular reabsorption of water, on the other hand, responds rapidly to changes in the secretion of the anti-diuretic hormone of the posterior pituitary (ADH) (30). In addition, there is probably another more slow-acting mechanism by which distal tubular adjustments to body hydration can be made (31).

Verney (32) has shown that intravenous injections of certain hypertonic solutions may stimulate the secretion of ADH. In dehydration, secretion of ADH is at or near maximal, and therefore little or no increase in secretion would be expected from the intravenous injection of mannitol or glucose. During osmotic diuresis and hydropenia, therefore, there would be little modification of the water or salt content of proximal tubular fluid by distal tubular mechanisms. The urine composition would then approximate that of proximal tubular fluid. Increased excretion of water would exceed that of sodium and chloride, and urinary concentrations of these ions would decline.

During water diuresis, by contrast, when ADH secretion and distal tubular reabsorption of water are depressed, intravenous hypertonic mannitol or glucose would be expected to produce a considerable increase in anti-diuretic activity. According to the degree to which distal tubular water reabsorption accommodated the increased volume of water being delivered from the proximal tubules, increased salt excretion would be accompanied by a rise or fall in urine flow and electrolyte concentration. Any chloruretic effect ADH itself may have (33-36) would contribute to these changes.

Verney (32) found that the cerebral osmo-receptors promoting ADH secretion do not respond to intracarotid injections of hypertonic urea solutions. Diureses caused by such highly diffusible substances as urea may therefore require an explanation other than that offered above. This problem is now under investigation (37).

## SUMMARY

Intravenous injection of 25 grams of mannitol during a large water diuresis may increase sodium and chloride excretion with no change, or even a decline, in urine flow. Intravenous injection of 25 grams of mannitol during hydropenia increases urine flow and salt excretion and decreases urine salt concentration. In one experiment, a large glucose infusion given during water diuresis increased salt excretion prior to, and in excess of, water excretion. Explanations of these phenomena are offered, based on recently advanced concepts of renal salt and water excretion.

Sharp & Dohme, Inc., kindly furnished the mannitol used in these studies.

The glucose experiment reported here was performed with the collaboration of Drs. D. W. Seldin and R. Tarail of this department, who are studying certain other aspects of osmotic diuresis.

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# Effects of Pituitrin and Exercise on a Water Diuresis

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THE EFFECTS OF PITUITRIN on the latent period of a diuresis invoked by the ingestion of water and on the nature of such a diuresis have been studied by Pickford (1) in the case of the dog, and by Hemingway and Peterson (2) in both dog and human being. This paper describes experiments carried out on over 50 normal human subjects.

## METHODS

The subjects, healthy medical students of either sex, were divided into four groups: *A*, 12 subjects; *B*, 20 subjects; *C*, 10 subjects; and *D*, 14 subjects. Each subject was used only once and took 800 cc. of water by mouth at the start of the experiments. All experiments were performed during the afternoon. *Group A* acted as a control and received no pituitary extract. *Groups B* and *C* received an intra-muscular injection of .000125 cc. and .00025 cc. of pituitrin (Parke Davis 10 U/cc.), respectively, at the time of taking the water. *Group D* received a similar injection of .000125 cc. of pituitrin when the diuresis was established. Within each group the subjects were paired off, one member of each pair took exercise consisting of running one quarter of a mile over rough ground, as soon as the diuresis has been established, while the other member of the pair took no exercise. The time taken to perform this exercise was between 60 and 90 seconds. Urine was collected without catheterization in 15- to 20-minute periods. Diuresis was judged to have been established when the urine flow had increased 42 per cent over basal level (3). Samples were analyzed for chloride by the method of Sendroy (4).

## RESULTS

*Latent Period of the Diuresis.* In figure 1 are plotted the latent periods for the four groups of subjects. The mean time for diuresis to appear for the *Group A* subjects was 0.75 hr. (range 0.25-1.25 hr.); for *Group B* 1.08 hr. (range 0.75-1.5 hr.); for *Group C* 1.13 hr. (range 1.0-1.25 hr.). *Group D* subjects who had received no pituitrin during this period, and are comparable

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with the *Group A* subjects in this respect, showed a latent period of 0.66 hr. (range 0.5–0.75 hr.). The pituitrin lengthened the latent period in all those subjects who received their injection at the time of taking water, the effect being more marked in the *Group C* subjects.

*Duration of Diuresis.* In figure 2 is plotted the duration of diuresis for the subjects of all four groups. This period is measured from the onset of diuresis (as measured by Adolph's criteria, 3) until the urine flow returned to normal again. It will be seen that when the pituitrin is given with the water (*Groups B* and *C*) the diuresis is very much shortened, but when it is given with the diuresis established the time taken for the urine flow to return to normal again is lengthened very considerably. It will also be noticed (figure 2) that the

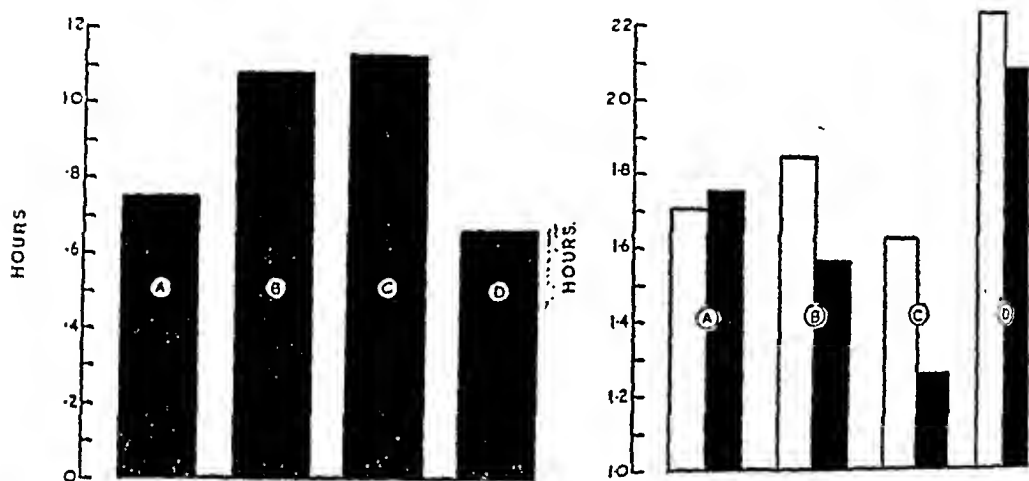


Fig. 1. (left) LATENT PERIOD of a diuresis following the ingestion of 800 cc. water. Dosage given in text.

Fig. 2 (right). DURATION OF A DIURESIS following the ingestion of 800 cc. water. White blocks, subjects taking exercise; black blocks, subjects taking no exercise. Dosage as given in text.

taking of exercise annulled the pituitrin effect in *Groups B* and *C*, while in *Group D* the diuresis was prolonged even more.

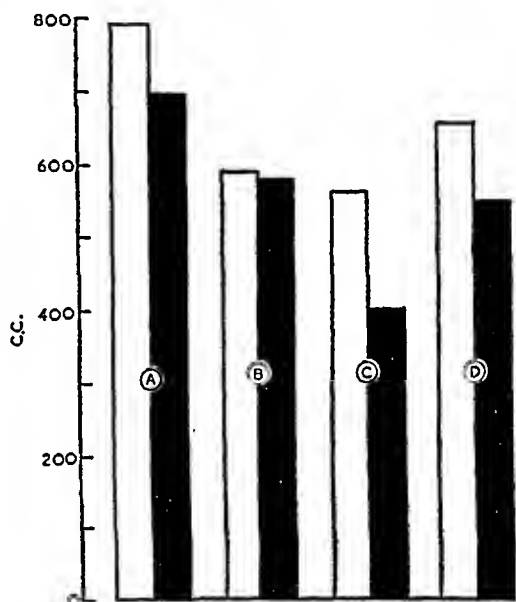
*Volume of Water Recovered During the Diuresis.* In figure 3 is plotted the mean volume of urine recovered during the diuresis by the subjects of each of the four groups. It will be seen that the pituitrin (*Groups B* and *C*) reduced the volume returned considerably, the effect being much more marked in *Group C*. *Group D* subjects also showed a decrease in returned volume of the same order as *Group B*.

When exercise was taken the volume returned by each group of subjects receiving pituitrin was increased and there was no longer any significant difference between *Groups B* and *C*. The *Group D* subjects returned a greater volume than subjects receiving a similar dose of pituitrin at the time of taking the water. This would appear to be because the volume effect of the diuresis has already become established by the time the hormone was administered,

and so one would expect *Group D* subjects to show an effect between *Groups A* and *B*.

**Chloride Excretion.** The rate of chloride excretion was raised in all the subjects receiving pituitrin and in figure 4 chloride and water excretion are illustrated for the non-exercising subjects. Those in *Group B* have a maximum chloride excretion five times as high as those in *Group A*, while those receiving the double dose of pituitrin, *Group C*, have a chloride excretion between these two groups, with a maximum only twice that of the controls. While chloride excretion in *Groups A* and *B* showed the typical rise with diuresis, *Group C* subjects showed a relatively constant excretion with only a slight rise with the

Fig. 3. VOLUME OF WATER recovered during the diuresis. *White blocks*, subjects taking exercise; *black blocks*, subjects taking no exercise. Dosage as given in text.



onset of diuresis following an initial fall. It is difficult to draw any conclusion from the results of the *Group C* subjects because of the high initial level of excretion, due to a very high excretion on the part of a few members of this group.

In figure 5 the curve for the subjects receiving no pituitrin, *Group A*, is taken from only one member of the group. The curve of diuresis is typical in its form but smaller than the average in magnitude; the average volume of diuresis for these subjects being slightly higher than that for the non-exercising subjects. When exercise was taken chloride excretion fell very markedly in all cases, except in subjects in *Group C*, in spite of the fact that inhibition of urine flow did not occur (fig. 5). The subjects receiving no pituitrin, *Group A* (of whom only a typical example is represented in fig. 5), all showed a fall in chloride excretion. The *Group C* subjects receiving the double dose of pituitrin

showed no fall in chloride excretion following exercise, and urine flow continued to rise. Where the injection was given immediately before the exercise (*Group D*) chloride fell sharply but at once returned to a higher level; urine flow continued to rise and only fell after a period of 30 minutes. It will be seen from the shape of the curves for urine flow that the effect of the pituitrin

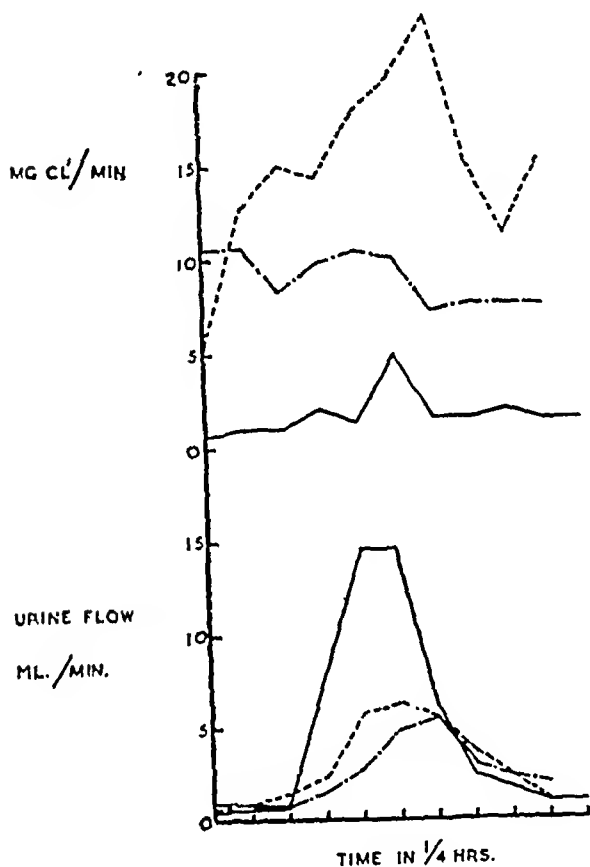


Fig. 4. CHLORIDE AND WATER EXCRETION in subjects taking no exercise. 800 cc. water ingested at zero time. — Group A; - - - Group B; — · — Group C.

is to prolong the diuresis and this prolongation does not appear to be affected by the taking of exercise.

#### DISCUSSION

It would appear that the pituitary extract lengthens the period between the taking of water and the appearance of the diuresis and also shortens the actual duration of the diuresis. The volume of water recovered in the diuresis is also reduced; presumably the remaining water load is excreted at such a slow rate as to make no appreciable difference to the basal urine flow and in this way actually extends the period over which the water drunk is returned. Exercise appears to annul this pituitrin effect, more of the water load being returned during the period classified as the diuresis. In the case of the single dose of pituitrin the length of diuresis is increased by the taking of exercise.

Chloride excretion is consistently increased by pituitrin, the effect being more marked in the case of a single dose than in the case of the double dose. When exercise was taken chloride excretion fell although evidence from the

subjects receiving the double dose of pituitrin and those receiving the injection at the time of exercise suggests that pituitrin counteracts this effect and keeps the chloride excretion more nearly constant.

### SUMMARY

The effects on a water diuresis of a dose of pituitrin given either with the water or when the diuresis was at its height has been investigated in 50 normal human subjects. a) Pituitrin lengthens the latent period of the diuresis. b) Pituitrin shortens the diuresis and reduces the amount of the ingested water

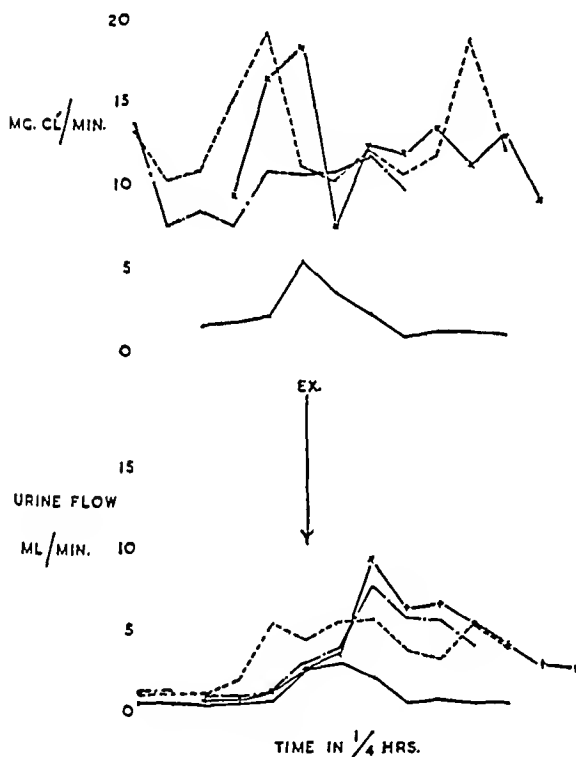


Fig. 5. CHLORIDE AND WATER EXCRETION in subjects taking exercise. 800 cc. water ingested at zero time. Exercise taken at point marked by the arrow. — Group A; - - - - - Group B; — · — Group C; — X — Group D.

recovered. Both of these effects appear to be counteracted by the taking of exercise. c) Pituitrin enhances the excretion of chloride and counteracts the exercise effect on the electrolyte. d) These effects of pituitrin may account for some of the differences of chloride and water excretion seen in a previous series (5).

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# *Renal Excretion of Lactic Acid in Exercise*

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THE EXCRETION OF LACTIC ACID in the urine following muscular exercise was reported by Spiro (1) in 1877-78. With the demonstration by Fletcher and Hopkins (2) that lactic acid accumulates in contracting muscles, attention was directed to its rôle in the contraction process. The changes in blood lactate concentration accompanying exercise have been extensively investigated, but quantitative studies on the renal excretion of lactate have been few. Liljestrand and Wilson (3), Jervell (4) and Johnson and Edwards (5) reported that the amount of lactate recovered in the urine after exercise accounts for not more than 2 per cent of the amount which disappears from the blood, but their data shed little light on the mechanism of the renal excretion of lactate. Jervell's suggestion (4) that lactate is actively secreted by the renal tubules is not consistent with the small amount of lactate which he recovered in the urine. Hewlett, Barnett and Lewis (6) reported that urine lactate concentration rises only when blood lactate concentration exceeds 30 to 40 mg. per cent, which suggests that lactate is a threshold substance, similar to glucose. Craig (7) determined the renal clearance of lactate in dogs given large amounts of sodium lactate by mouth or intravenously. He reported nearly complete tubular reabsorption of lactate at plasma levels below 100 mg. per cent.

In spite of the paucity of information concerning the mechanism of the renal excretion of lactate, urine lactate is frequently used as an index of lactic acid production in exercise. Accordingly, the present study was undertaken in an attempt to provide data on the following points: 1) the renal threshold for lactate, 2) the relation between maximal blood lactate concentrations and total urine lactate over a wide range of blood lactate concentrations and 3) the accuracy with which urine lactate reflects total lactate production in exercise.

## METHODS

The experimental subjects were 2 distance runners on the University track team. The experiments were performed during the season of competition, so that the subjects were in excellent training and able to push themselves to high blood lactate levels. The exercise consisted in running on a motor-driven treadmill for 2 to 15 minutes, at zero grade and at speeds of 10 to 16 miles/hr. A total of 72 experiments was performed, in which the maximal

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blood lactate concentration ranged from 25 to 116 mg. per cent. Resting lactate excretion was measured on urine samples collected before exercise. The bladder was emptied just before the exercise began and urine samples were collected at intervals of 10, 20, 40 and 60 minutes from the beginning of exercise. The water intake of the subjects was adjusted to insure adequate urine volumes; in a number of experiments the exercise was performed during water diuresis in order to obtain a wide range of urine flow rates. Lactic acid was determined by the method of Barker and Summerson (8) on the urine samples and on finger-prick blood samples timed to coincide with the urine samples.

### RESULTS

The relation between post-exercise blood lactate concentration and total urine lactate in a one-hour post-exercise period is shown in figure 1. In each case the line drawn through the plotted points was derived from the class interval averages and the point of intersection with the abscissa is the theoretical lactate threshold. It is apparent that urine lactate is proportional to blood lactate concentration when the latter exceeds the threshold value of approximately 60 mg. per cent. There is no sharp break in renal excretion rate at the threshold blood lactate concentration. A small amount of lactate is present in resting urine samples and the excretion rate increases hyperbolically with increasing blood lactate concentration, becoming linear at a blood concentration of approximately 70 mg. per cent.

The regression equations for prediction of blood lactate from urine lactate are:

$$(\text{Subject A}) B = .09 L + 54.2 \quad (\text{Subject B}) B = .10 L + 47.5$$

where  $B$  = post-exercise blood lactate in mg. per cent and  $L$  = milligrams of lactate in a one-hour post-exercise urine sample.

The lactate clearance was calculated from the blood and urine data in a number of experiments. The resting clearance is 1 to 2 ml/min. In exercise the maximal clearance rate rises as the blood lactate concentration rises. In moderate exercise with a blood lactate concentration of approximately 50 mg. per cent, the clearance is 6 to 8 ml/min.; in exhausting exercise with blood lactate concentrations of 100 to 115 mg. per cent, the lactate clearance is 8 to 12 ml/min. during the exercise period and it may rise to 15 to 20 ml/min. in the early part of the recovery period. These data must be interpreted with caution in view of the known decrease in renal blood flow which accompanies exercise. Thus, White and Rolf (9) reported a decrease in renal blood flow to 20 or 25 per cent of the control level in short periods of exhausting exercise. If Trueta's concept (10) of the diversion of some of the renal blood flow into noneffective channels in exercise is accepted, the effective renal blood flow would be even less. Since the filtration fraction was not greatly altered in White and Rolf's experiments, it may be assumed that the excretion of lactate in our experiments is reduced in proportion to the decrease in renal blood flow. Thus a clearance

rate of 10 ml/min. during severe exercise would be equivalent to a rate of approximately 50 ml/min. with the same blood lactate concentration and normal resting renal blood flow rate. This agrees well with a calculated renal

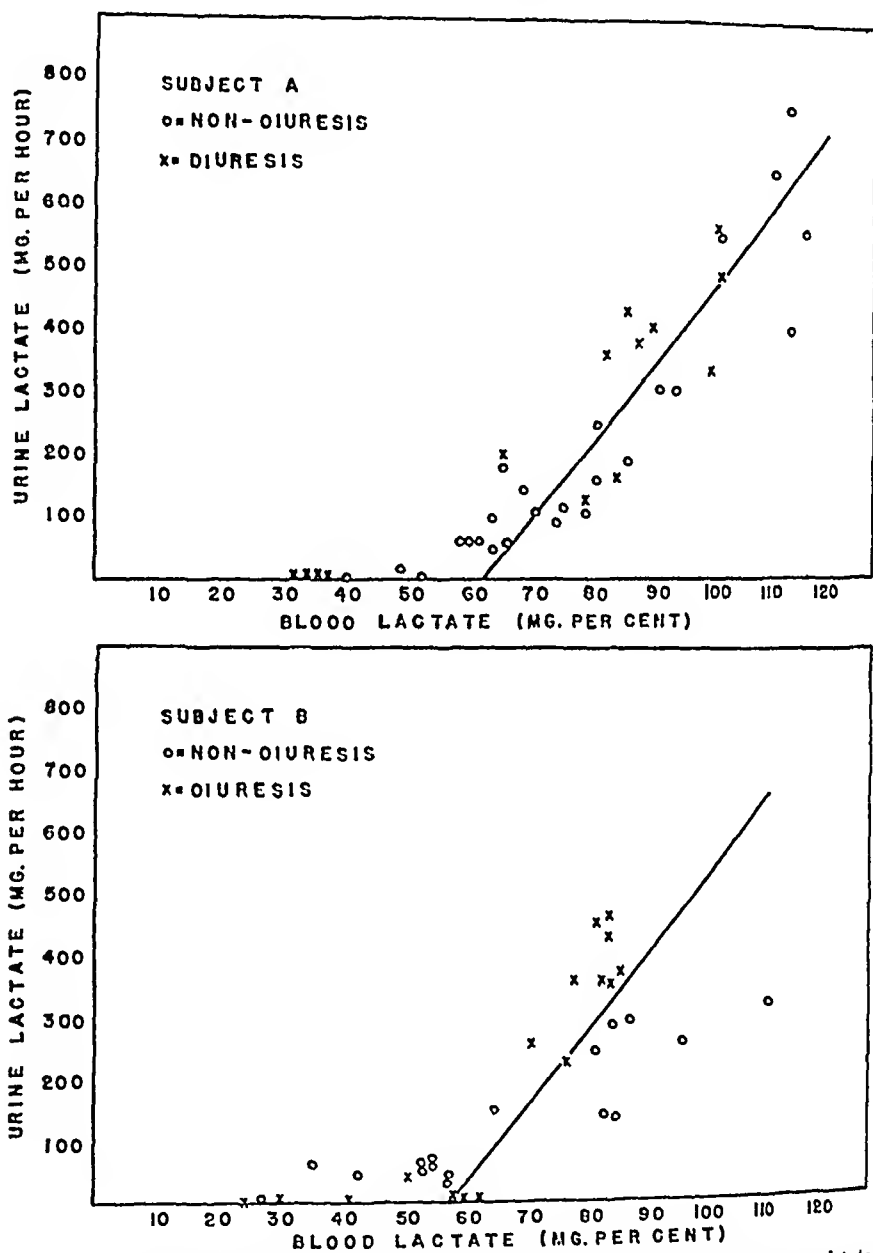


Fig. 1. RELATION BETWEEN POST-EXERCISE BLOOD LACTATE CONCENTRATION and total lactate recovered in the urine in a one-hour post-exercise period. In non-diuresis experiments subjects were normally hydrated; in diuresis experiments subjects drank one liter of water 60 to 90 minutes before exercise. The line drawn through experimental points is the best fitting line for the class interval averages.

threshold of 60 mg. per cent in which approximately one-half the filtered lactate would be reabsorbed when the blood concentration is 100 to 115 mg. per cent.

It is apparent from the data shown in figure 1 that the renal excretion of

lactate is also influenced by the urine flow rate. With the large urine volumes obtained when exercise was performed during water diuresis, the excretion of lactate was also increased. This is seen especially clearly in the data of *Subject B*.

Finally, it should be pointed out that the calculation of lactate clearance in these experiments is approximate, since the blood lactate concentration was hanging during the observation period. However, in the more exhausting exercise experiments, the blood lactate concentration changed very little during the first 10 minutes of recovery, so that clearances based on this period are reasonably accurate.

### DISCUSSION

The data presented above support the concept that lactate is filtered in the glomeruli and variably reabsorbed in the tubules. The apparent renal threshold is approximately 60 mg. per cent, but small amounts of lactate appear in the urine at blood concentrations below this threshold. Since the renal excretion of glucose has the same general features (11, 12) it is a plausible assumption that glucose and lactate are handled by the kidney in the same general manner. This would place the site of reabsorption of lactate in the proximal tubule. It may also be presumed that the threshold for lactate, like that for glucose, is variable both in different individuals and at different times in the same individual. This would account for some of the scatter of individual points about the line relating lactate excretion and blood lactate concentration.

The fact that renal excretion accounts for a very small proportion of the lactate which disappears from the blood in a post-exercise period is now understandable. 1) The amount of lactate filtered in the glomeruli is reduced by the drastic curtailment of renal blood flow which accompanies severe exercise. 2) With a threshold value of approximately 60 mg. per cent, fully one-half the lactate filtered in the glomeruli is reabsorbed in the tubules even in exhausting exercise. In moderate exercise the reabsorption fraction increases. The quantitative implication of these facts is made clear by a sample calculation. If one assumes a blood lactate concentration of 100 mg. per cent, a normal renal blood flow and no tubular reabsorption of lactate, the lactate clearance would be about 120 ml/min. If, however, the renal blood flow is reduced to 25 per cent of normal and the lactate threshold is 60 mg. per cent, the lactate clearance becomes  $0.4 \times 0.25 \times 120 = 12$  ml/min., the approximate value obtained in severe exercise in our experiments.

The accuracy with which urine lactate reflects total lactate production in exercise is limited by the variability in renal threshold and in the changes in renal blood flow in different individuals and even in the same individual at different times. At best it is a rough index of the severity of exertion.



## SUMMARY

Blood lactate concentration and total urine lactate during exercise and recovery were determined in 72 experiments on 2 subjects. The experiments covered a wide range of blood lactate concentrations and urine flow rates. The data support the concept that lactate is filtered in the glomeruli and variably reabsorbed in the tubules. The apparent renal threshold is approximately 60 mg. per cent, but small amounts of lactate appear in the urine at blood concentrations below this threshold. The lactate clearance is 1 to 2 ml/min. at rest and rises to 15 to 20 ml/min. in exhausting exercise. The clearance is increased during water diuresis.

Urine lactate is only an approximate index of total lactate production in exercise, due probably to variability in the renal threshold and in the renal blood flow changes in exercise in different subjects and in the same subject at different times.

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## *Effect of Body Position on Incidence of Motion Sickness<sup>1</sup>*

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IN CANADA our chief concern with the problem of airsickness was that occurring during flying training, particularly during early training at the elementary, air observer, or bombing and gunnery school stages. It was an important cause for 'cease training' during this period, and also a contributory factor in many other 'cease training' cases (1, 2).

In early surveys carried out in Canada it was shown that approximately one third of the aircrew experienced airsickness during the early part of flying training. The more careful the study, however, the more apparent it was that airsickness occurred in greater frequency than was commonly supposed. Some Canadian surveys have shown the incidence as high as 60 to 70 per cent during the first two weeks, if all signs or symptoms of airsickness were included (1). The incidence of 'cease training' due to airsickness ranged from approximately 1 to 6 per cent (1).

Prior to 1940 the problem of motion sickness was a subject of much speculation and little experimental work. Many theoretical explanations have been reported but only the labyrinthine theory is supported by substantial evidence. Since Baranay's original experiments in 1910, evidence has accumulated to prove that forces acting on the utricular portion of the labyrinth are chiefly responsible for the motion sickness syndrome (3).

It is apparent that during flight in an aircraft or glider many factors known to affect the incidence and severity of airsickness cannot be controlled. Consequently, laboratory devices capable of reproducing forces somewhat similar to those encountered in aircraft were employed in an effort to ascertain the fundamental etiology responsible for motion sickness. The majority of laboratory studies on motion sickness carried out by the R.C.A.F. have involved the use of swings. Correlation studies between air and swing sickness have shown that the signs and symptoms which develop on the swing are similar to those occurring in airsickness, but do not necessarily occur in the same individual (4).

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In approaching the problem, we decided to use a two-pole, manually operated type of swing. Later, various types of swings were used. Our first problem, however, was to familiarize ourselves with the syndrome of swing sickness, for at this time we knew nothing of simple swing sickness let alone the complex problem of airsickness.

These preliminary studies consisted of 1005 swing experiments showing the effect of some 14 different body positions and visual orientation on the incidence of swing sickness and are reported in this paper. Although later studies have added to our understanding of the etiology of motion sickness these initial results (5) remain substantiated (8) and consequently are published at this time without alteration.

### METHODS

In this study 1005 swing experiments are reported. In 155 of these the same subject was used on two occasions (and 8 men on 3 occasions), but never less than 7 to 10 days apart. The subjects were healthy young aircrew, between the ages of 18 and 32, who were awaiting posting to Elementary Flying Training School between the months of May and November, 1942.



Fig. 1. Swing used in the studies.

A swing similar to that described by Brown, McArdle and Magladery (6) (fig. 1) was employed. The supporting ropes were 14 feet in length and the frequency of the swing 14 per minute. The swing was operated manually and an attempt made to swing all the subjects through the same arc of 69 degrees. However, because of the variable human element in supplying the kinetic energy to the swing, it was impossible to swing each subject through exactly the same arc. An excursion of 17.2 feet, through which the swing moved, sub-

tended an angle of 69 degrees. The variation in excursion was estimated to be within 6 inches, which represents an angular difference of 2 degrees (i.e.,  $\pm 1^\circ$  for either end of the swing excursion.)

The subjects maintained the same position throughout all experiments. Each, without the aid of any mechanical device, maintained his head in a constant but natural attitude for any body position. He was permitted to look about, moving the eyes only. The relation of the head with respect to the body in general was defined in terms of head topography.

No attempt was made to control the time of swinging in relation to meals since in each group experiments were carried out at half-hour intervals through-

out the day. With one exception (*group 2*) all groups of men were swung for 30 minutes unless illness intervened. In earlier experiments many men were swung to the point of vomiting. However, in later studies, extreme pallor, sweating and nausea in addition to the subject's request to have the swinging stopped were accepted as evidence that the vomiting stage was imminent.

The experiments included 14 groups of men swung under the various conditions and positions shown in table 1. In the prone and supine position the subject assumed a position of maximal comfort, on the platform of the swing

TABLE 1. EFFECT OF POSTURE ON THE INCIDENCE OF SWING SICKNESS

GROUP NO.	ATTITUDE OF SUBJECT	EYES	PLANE OF LATERAL SEMICIRCULAR CANAL	NUMBER OF MEN	TYPE I NO SYMPTOMS AFTER 30 MIN. ON SWING	TYPE II 30 MIN. ON SWING, SUBJECT PALE & NAUSEATED	TYPE III SWING SICK NAUSEA AND VOMITING IN LESS THAN 30 MIN
					<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
1	Supine	Open	+107	126	90.0	5.0	5.0
2	Supine (20 min.)	Closed	+107	41	90.0	5.0	5.0
3	Supine	Closed	+107	45	84.5	4.5	11.0
4	Prone	Open	-40	40	42.5	7.5	50.0
5	Prone	Closed	-40	38	34.0	13.0	53.0
6	Sitting facing operator	Open	+21	171	58.5	14.0	27.5
7	Sitting facing operator	Closed	+21	90	40.0	9.0	51.0
8	Sitting facing operator room dark	Open	+21	80	56.0	5.0	39.0
9	Sitting facing operator with goggles	Open	+21	80	35.0	7.5	57.5
10	Sitting facing operator (Barany Chair)	Open	+21	73	41.0	18.0	41.0
11	Sitting facing operator—swing covered	Open	+21	50	12.0	24.0	64.0
12	Sitting side position on chair	Open	+21	50	76.0	12.0	12.0
13	Sitting side position on platform	Open	+21	41	56.0	20.0	24.0
14	Standing facing operator	Open	+11	80	60.0	12.5	27.5

and maintained this throughout the period of swinging. In the face down position, pillows on either side of the face protected the nose from trauma. The attitude of a subject in the sitting position with eyes open and facing the operator is shown in figure 1. The other sitting positions were comparable except that vision was modified by dark goggles which allowed about 3 per cent light transmission, by closing the eyes for the duration of the swing or by completely darkening the room. In the dark room experiments, however, it was possible after a short time to discern roughly surrounding large objects. The position of the swing was manifest to the operator by means of a pin point of light (covered flash light) attached to the foot of the swing (fig. 1). In order to ascertain whether additional labyrinthine stimulation appreciably altered a

man's swing susceptibility, 73 men (*group 10*) were given the Barany Chair test 10 minutes to one hour prior to swinging. This consisted to rotating the subject 10 times in 20 seconds with the head tilted forward  $30^\circ$  and 10 times in 20 seconds tilted a further  $99^\circ$  forward.

In *group 11* the subject was completely enclosed in a cabin-like arrangement by means of canvas sheeting fastened to the four suspension ropes (the top also being covered). The subjects were swung inside the cabin-like arrangement in the sitting position facing the operator and with the eyes open. By this arrangement visual shifting from object to object in the room, parallax, and the wind or breeze effect on the subject due to swinging were removed.

In *group 12* the subject was seated on a chair fastened to the platform of the swing and was thus elevated 18 inches. In *group 13* the same attitude was assumed except that the subject sat on the platform itself. In each of these two groups of experiments the subject was instructed to face in the direction he was seated and swung sideways in this manner. In the standing position (*group 14*) while facing the operator, a special harness supported from the four suspension ropes loosely encircled the subject in such a way that if he became dizzy he could not fall from the swing.

## RESULTS

1. The incidence of motion sickness for each of the various positions studied is shown in table 1.

2. *Variation of Plane of Lateral Semicircular Canal.* Since the position of the head was not fixed by any mechanical device but voluntarily held in the most natural position peculiar for any particular body attitude, a special study of 60 airmen was made to ascertain the approximate position of the lateral semicircular canals, and therefore the labyrinth in general. The criterion employed was a line drawn from the most prominent tip of the antitragus to the corresponding outer canthus. The angle this line subtends with the horizontal approximately defines the plane of the lateral semicircular canals in relation to the swing platform. The angle varies from subject to subject and with each subject in each of the four positions studied, namely, the supine, prone, sitting and standing. With very few exceptions the angles on either side of the head in any position approximate one another by 2 to  $3^\circ$ . For sake of uniformity and also as a working basis, reference is made only to the right side of the head. The average plane of the lateral canal in degrees from the horizontal, and the range are shown in figure 2. In the supine position the right lateral semicircular canal was directed upward and backward at an angle of from plus  $96^\circ$  to plus  $120^\circ$  or on the average  $107^\circ$ . In order to effect the maximal vertical acceleration in the direction of this canal the head of each subject should be tilted forward  $17^\circ$  on the average. In the prone position this same canal was directed downward and forward an average of minus  $40^\circ$ . To effect maximal

vertical acceleration on this canal with the body prone the head should be further flexed an average of  $50^\circ$ .

With the subject sitting, the topographic marking of the right lateral semi-circular canal was directed upward and forward an average of  $+21^\circ$  (fig. 2). Hence to effect maximal horizontal acceleration the head of each man should be tilted forward an average of  $21^\circ$ .

In the standing position the topographic markings were in the same direction as with the subject sitting but the angle formed with the horizontal was considerably decreased and approximated  $+11^\circ$ .

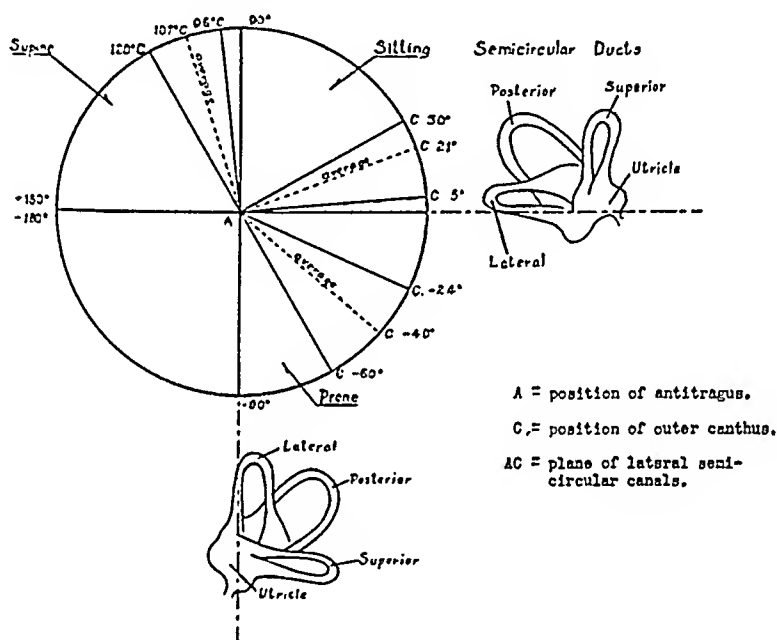


Fig. 2. Relationship of semicircular canals to the horizontal for sitting, supine and prone positions (represented by a line from antitragus to corresponding ureter cauthus). Right side.

3. *Environmental Factors in Relation to Swing Sickness.* Environmental factors which may have affected the incidence of swing sickness were noted throughout this study. These related to apprehension, the month during which any phase of the work was carried out, the temperature of the room in which the swing was located, the time of the day in relation to meals when swinging was carried out, as well as the natural variability of a man's susceptibility on different occasions.

From table 2 it is apparent that the group incidence (different groups) of Type I responses does not vary greatly in different months or seasons except during the month of June. During June the percentage of Type II responses was increased considerably and so reduced the percentage of men showing no

symptoms in the sitting, eyes open, position. No reason could be found for this difference.

It would appear that time of day is of little importance so far as swing susceptibility is concerned. There was no significant difference in the morning as compared to afternoon incidence in 171 men in the sitting and 126 men in the supine position. The incidence of swing sickness in any one position did not vary significantly in groups of men swung shortly before as compared to shortly after a meal.

During the studies it had been noted that individuals exhibited different swing reactions when reswung under similar conditions. Data relating to 26

TABLE 2. INCIDENCE OF SWING SICKNESS DURING VARIOUS MONTHS (DIFFERENT GROUPS)

MONTH	POSITION OF SUBJECT	TOTAL NO. OF MEN	SWING REACTION			ROOM TEMP. RANGE	AVERAGE MID-DAY TEMP.
			1	2	3		
			%	%	%	°F.	°F.
May.....	Supine, eyes open	86	91	6	3	74-80	58.2
June.....	Supine, eyes open	24	88	8	4	72-78	62.4
October.....	Supine, eyes open	16	88	0	12	68-78	48.7
Total.....		126	89	6	5		
June.....	Sitting, eyes open	80	48	22	30	72-78	62.4
July.....	Sitting, eyes open	47	69	3	28	74-78	69.6
October.....	Sitting, eyes open	40	70	8	22	68-78	48.7
Total.....		167	59	14	27		

TABLE 3. TREND OF SECOND SWING REACTION AS COMPARED WITH INDIVIDUAL FIRST SWING REACTION

SWING SUSCEPTIBILITY	NO. OF MEN	PER CENT
Not changed.....	13	50
Less.....	6	23
Greater.....	6	23
Variable.....	1	4

such men showed that 13 men became ill on each occasion but not necessarily the same men. The interval between swings was never less than 7 days and was on one occasion as long as 73 days. It was apparent that for any individual a single swing is not necessarily a measure of his swing susceptibility. However, when the individual reactions are considered as a group, the group incidence of Type I swing sickness was not altered although there was a lowering of Type III and a rise of Type II reactions for the group as a whole.

The change in swing reaction of these 26 individuals is shown in table 3. Fifty per cent showed no change in swing susceptibility regardless of the type of original swing reaction. The swing reaction of 23 per cent was less severe, while in an equal percentage it was more severe on the occasion of the second

as compared with the first swinging. Only 10 of the 26 men considered in this particular analysis were swung on more than 2 occasions at intervals of 7 days or longer. Of this number only one man showed a variable reaction. In view of the paucity of cases the significance of this finding is questionable.

The factor of apprehension in swing experiments does not appear to be very important. In these experiments 44 subjects were swung in the sitting position, eyes closed, and 7 to 10 days later swung again in the supine position, eyes closed. These experiments were done at a time when large numbers of men were being swung in the most susceptible positions and the incidence of sickness was high. The result of the first swinging (sitting, eyes closed) showed 63.8 per cent swing sick within 30 minutes. The group was not informed that they were to be swung again until 7 to 10 days later when they returned obviously expecting to undergo the same unpleasant sensation, since the incidence in other groups swung during this time had remained the same. Under these circumstances the psychological factors would favor a high susceptibility to swing sickness. No explanation of the possible difference that might occur in susceptibility was given, yet only 11.4 per cent of this same group became ill when swung in the supine position, eyes closed. All of the men who became ill in the supine position had shown the same reaction during the first swinging in the sitting position.

#### DISCUSSION

In this report the position of the subject, with particular reference to the plane of the lateral semicircular canals and contiguous structures, and the effects of vision on the incidence of swing sickness are considered. Relevant data in relation to meals, time of day, month of year, individual and group variability in swing susceptibility when reswung as well as the effects of apprehension are also presented because of their importance in the interpretation of the effect of posture and vision on the incidence of swing sickness. Following these studies in which the importance of head position and not body position per se was apparent, similar findings were obtained by altering head position only.

From the study of the effect of environmental factors, it was apparent that the variations in group incidence in these studies were primarily due to variations in posture (position of the head) and visual orientation.

The marked differences in incidence of swing sickness in the various groups studied are apparent from table 1. In the supine position, eyes open, only 5 per cent of the subjects became ill in 30 minutes whereas in the sitting position, with the eyes open, this increased to 27.5 per cent. The relationship of vision was apparent with subjects swung in the sitting position with eyes closed: 51 per cent of this group becoming ill within 30 minutes. Similarly with the subjects wearing black-out goggles (as used in night visual acuity test) the per-



centage that became ill was high (57.5%). In the darkened room, however, the incidence also in the sitting position was intermediate between the groups swung with eyes open and with eyes closed (39%).

The incidence of swing sickness in any position was found to be increased when the visual perception was reduced by closing the eyes, in a darkened room or wearing glasses. Furthermore, with the subject completely enclosed in a tent-like cabin arrangement, the incidence increased to the maximum found in these experiments. Under such conditions, the subject could see about the interior of the enclosure but was isolated and lost complete visual contact with the ordinary stationary surroundings. Under these conditions the severity and incidence of symptoms were both increased.

The least susceptible position encountered was the supine with eyes open, whereas the prone position with the eyes open was a very susceptible one. Since in both, the effect of vertical acceleration on the cardiovascular system was minimized, the resultant swing sickness must be primarily due to labyrinthine stimulation. The difference in susceptibility therefore must have been due to the position of the labyrinth with reference to the horizontal rather than the position of the body per se.

It would appear that the incidence of swing sickness should have been greater in *group 6* (sitting) than in *group 14* (standing) since by shortening the radius (*group 14*) the effective stimulus (i.e. the quantity of vertical G. change) was reduced. However at the same time the plane of the lateral semicircular canals was changed from  $+21^\circ$  in the sitting to  $+11^\circ$  in the standing position which, in view of the results obtained with other groups, may account for this similar incidence. The results obtained with *groups 12* and *13* would support this interpretation. Although the plane of the lateral semicircular canal was  $+21^\circ$  in both *groups 12* and *13* the incidence of sickness was somewhat reduced when the radius (i.e. fulcrum to labyrinth) was shortened 18 inches by swinging the subject seated on a chair.

Throughout this report reference has been made only to the lateral or horizontal semicircular canal for the sake of orientation of the labyrinth in general. From figure 2 the relationship of the labyrinth to the horizontal plane can be visualized for the various positions studied. The vertical canals most closely assume a horizontal position in the supine position. The incidence of swing sickness was lowest in this group. In the prone position assumed by our subjects the vertical canals were not horizontal and may alone account for the marked increase in swing sickness in this position. The incidence of swing sickness can be increased significantly if additional labyrinthine stimulation is given to the semicircular canals prior to swinging (*group 10*) by means of the Barany Chair.

It is apparent that stimulation of the vertical semicircular canals is more likely to produce sickness than stimulation of the horizontal canals and that by exposing them to a minimum of acceleration the least motion sickness follows.

Tait and McNally (7) suggest that the four vertical canals be called a gravity set because they respond to tipping movements out of the horizontal plane. They showed that the vertical canals are closely associated with the utricular maculae, the horizontal canals constitute a non-gravity set and respond to turning about a vertical axis, to which stimulation the utricular maculae are irresponsive (7).

It would appear from a consideration of these experiments that swing sickness is primarily the result of a specific labyrinthine stimulation which can be inhibited considerably by visual orientation. This stimulation of the labyrinth initiates the train of events manifest by nausea, vomiting and cardiovascular changes.

#### SUMMARY

In these experiments 825 men were used in a total of 1005 swing experiments. The men were swung in 14 different positions and the incidence of swing sickness noted for each group. The incidence varied with different body positions and visual orientation and was greatest when accelerative forces were acting in the plane of the vertical semicircular canals.

The maximal incidence of swing sickness occurred in the sitting position with the subject completely enclosed in a cabin-like arrangement. The minimal incidence occurred in the supine position with the eyes open. The group incidence did not change when the same subjects were reswung at an interval of 7 days or longer, although individuals varied in their swing susceptibility when swung on different occasions. The time of day, meals, room temperature and apprehension did not appear to be factors affecting group susceptibility.

These studies support the thesis that motion sickness is primarily a labyrinthine disturbance. This effect on the labyrinth can be modified considerably by visual orientation. The subsequent train of events characterized by nausea, vomiting, pallor, sweating, weakness and dizziness are the result of this stimulation.

The marked difference in swing sickness observed in these experiments suggest the supine position as the least susceptible. Consequently the adoption of the supine, or any position in which the vertical canals are horizontal, may be of value in the transportation of air-borne troops.

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## Basal Metabolism at the Menopause

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GLANDULAR IMBALANCE is widely recognized as accounting for the symptoms observed at the menopause, but the exact rôle of most of the hormones is still in doubt. It has been established that there is failure of the ovarian hormones, together with excessive secretion of the follicle-stimulating and luteinizing hormones of the pituitary (1, 2). It has been suggested that excess of prolactin A produces hot flashes; but the amount of prolactin A in women suffering hot flashes is not greater than in other women at the menopause (2); moreover, doses of estrin sufficient to relieve the hot flashes are not enough to diminish the amount of prolactin A significantly (3). Women exhibiting hot flashes react violently and abnormally to small doses of epinephrine, while other women react in the usual fashion (4, 5). It is not known what causes the increased sensitivity.

Thyroid activity at the menopause is of course lower than in youth but in most instances appears to be within normal limits (6). In a small percentage of cases it exceeds  $\pm 10$  per cent (7-10). Muehlbach (6) reports blood cholesterol levels high during the menopause but falling thereafter. Although the cyclic pattern of BMR is well known in young women, it does not appear to have been studied at middle age.

This report is concerned chiefly with basal metabolism at the menopause.<sup>1</sup> It includes BMR and cycle length in one subject over 9 cycles at age 35, 24 cycles at 45 to 47, one cycle at 48 and a few observations at age 60; also in another subject, BMR and basal temperature over 3 cycles at age 46 to 47, together with a record of cycle lengths from age 41 to 57. A few observations were made on hot flashes.

### RESULTS

The average BMR of the first subject at various ages is shown in table 1. At age 34 in a northern latitude (Stockholm) the average BMR was -4 per cent of the Harris-Benedict standard (11). At 35 in a hot climate (New Orleans) the average fell to -8 per cent (12). Ten years later in a temperate

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TABLE 1. AVERAGE BMR OF MEC

DATE	PLACE	AGE	WT. KG.	BMR		DEVIATION FROM STANDARD		CAL/SQM/HR.
				O <sub>2</sub> /min.	Cal/hr.	H-B %	Aub-Dubois %	
1922-3	Stockh.	34	60.5	190	54.6	-4	-8	34
1923-4	N. O.	35	60	178	51	-8	-13	32
1933-4	Clevel.	45	74.4	185	53.3	-14.5	-16	30.3
1933-4	"	45	71.5	182	52.4	-16	-16	30.3
1934-5	"	46	71.5	163	45.9	-17	-26	26.8
1934-5	"	46	59	155	44.4	-18	-23	28
1935-6	"	47	58.4	166	47.5	-13	-17	30
1936-7	"	48	63.4	169	48.6	-12	-17	29.8
1948	"	60	66.1	176	50.7	-6	-9	30.2
1948	"	60	62.5	175	50.5	-4	-9	30.1

TABLE 2. CYCLE LENGTHS AT THE MENOPAUSE

AGE	MEDIAN	AVERAGE	RANGE	SEQUENCE	
MEC					
34	25	24.7	22-27	(incomplete record)	
35	27	26	25-27		
45	24	23.8	20-35		
46	31	38	23-84		
47	41	41.5	31-48		
48	291	291	291		
EMR					
41	25-6	28	13-36	24 13 21 28 25 60 34 36 16 16 36 26	
42	25-6	25	18-28	28 26 25 25 23 28 26 26 24 25 18 26 25 23 26	
43	25-6	26	24-29	28 25 28 25 26 26 26 29 25 24 24 27 27 25 27	
44	24-5	25	24-27	24 26 25 24 24 25 25 25 26 27 24 25 24	
45	25	25	23-29	24 26 25 24 29 27 24 23 26 26 25 24 23 25 25	
46	25-6	25.6	23-30	26 26 28 28 23 28 22 25 26 30 25 23 25 24	
47	25	25.4	21-28	25 26 34 26 23 24 25 24 28 25 20 26 24 26	
48	25	26	18-27	21 26 27 25 26 28 25 27 24 22 25 27 24 27 24	
49	24	24.5	18-27	26 23 27 18 26 21 22 24 25 22 26 24 23 25 26	
50	24-25	24.4	15-27	27 23 23 15 23 27 27 23 27 24 25 28 26 22 26	
51	No record				
52	24-5	24	21-36	27 25 24 22 26 24 21 30 22 28 23 36	
53	24	37.3	19-89	89 19 47 20 24 23 60 22 31	
54	25	36.8	14-70	41 27 25 14 24 54 67 25 70 21	
55	34-45	41	15-70	34 45 15 70	
56	No record				
57	Two cycles of uncertain length.				

climate (Cleveland) at age 45, the average BMR dropped to -14.5 and then to -16 per cent, and the body-weight which had been high at 43-44 fell slightly (3 kg.). The next year at age 46 the average BMR dropped to -18 per cent

and the weight fell sharply (12.5 kg.). At age 47 the BMR rose to  $-13$  per cent and weight remained low. At age 48 low estrin medication was started and weight increased by 5 kg., but BMR remained low ( $-12\%$ ). The calories per square meter per hour shown in the last column of the table show the same curious relation to weight loss, being lower as weight was lost and rising slightly as it was regained. At age 60 BMR was  $-6$  per cent and weight had increased a further 3.3 kg. Later in the 60th year weight dropped owing to muscular exercise and the average BMR became  $-4$  per cent.

Cycle length over these years for our two subjects showed the expected irregularities (table 2). The usual cycle length for the first subject up to age 36 was 27 to 28 days with occasional variation, 25 to 31 days. At age 45 the median was 24 days and the range 20 to 35 days. At 46 the median was 31 and the range 23 to 84. At 47 the median was 41 and the range 31 to 48. At 48 there was only one cycle, 291 days. Briefly, the change in cycle length involved first a shortening, then interpolation of occasional long cycles which gradually increased in number, and then rather abruptly a last very long cycle. In the second subject we have a continuous record covering ages 41 to 57, except for two years; and this we present in detail since such continuous records are rare (13). In this subject at age 41 the cycle length median was between 25 to 26 days and the range was 13 to 36. From 42 to 47 there was little change. From 48 to 52 the median shortened slightly and the range was a trifle wider. At 53 the first very long cycles appeared, but from 53 to 55 the median remained short although the range was very wide. At 57 there were two long cycles of which no record was kept. The general pattern of change in cycle length is similar in both subjects except in the number of years required and in the age at which menstruation ceased.

The BMR pattern within the cycle was studied chiefly in the first subject. At ages 34 to 35 the pattern was that typical of young women. In each cycle there were two low points, one during the menstrual period and the other about mid-way of the cycle; and two high areas, one of about 8 days' duration immediately after the menstrual period, and the other in the last 6 days of the cycle. These high areas presumably indicate secretion of estrin and progesterin. Figure 1 shows a composite graph of 5 cycles, based upon data already published (12). The difference between the maximum and minimum BMR levels per cycle was 19 cc.  $O_2$  per minute.

At age 45 (fig. 2) the pattern was similar, but in the shorter cycles (23d) the second high area was broken and the maximum-minimum difference was 15 cc. in the longer cycles (26d) the first high area was broken but the second high area was normal, and the max-min. difference was 21 cc. If the high areas represent estrin and progesterin secretion, this would mean irregular secretion sometimes of one, sometimes of the other hormone. Ovulation occurred

at about the 14th day, as compared with the 17th day at age 35, although at both ages it varied between the 12th and the 20th day.

At age 46 (fig. 3) the pattern was still clear in the short cycles (25d) but was less clear in the longer cycles (45d), although the latter suggest two high areas developing irregularly. The longest cycle, occurring at age 46 (Fig. 4), showed a very uneven and delayed development of the first high area and a second high area of greater stability. Whether or not these two high areas

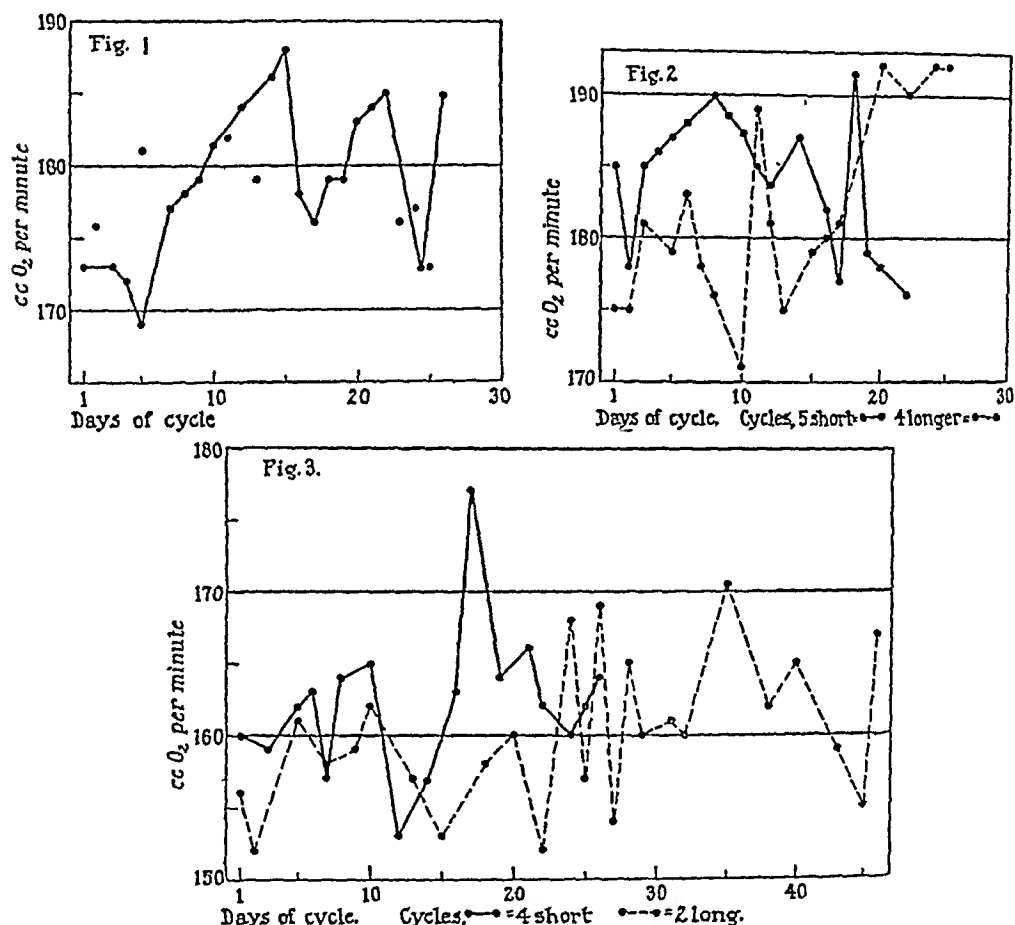


Fig. 1. MEC, age 35. Composite graph of 5 cycles

Fig. 2. MEC, age 45. Composite graphs of 5 short and 4 longer cycles

Fig. 3. MEC, age 46. Composite graphs of 4 short and 2 long cycles

correspond to the standard pattern in youth is doubtful. They may be parts of an estrin-produced rise which develops slowly and unevenly. This pattern of the long cycle resembles that of a 30-day cycle observed in the second subject at age 46 (fig. 6) in which only one delayed high area occurred. Two other cycles in the second subject at age 47, followed by means of basal temperatures, also appear to show delayed estrin production and no progestin (fig. 7). At age 47 in the first subject (fig. 5) short cycles showed the familiar pattern, though with the first high area irregular; the longer cycles showed two.

high areas both of which were delayed and irregular. The max-min. difference was 20 cc. Summarizing, it may be said that the usual cyclic BMR pattern characteristic of young women also occurs in the early years of the menopause, but toward the end of the menopause both high areas develop with increasing irregularity, which finally obscures any division between them.

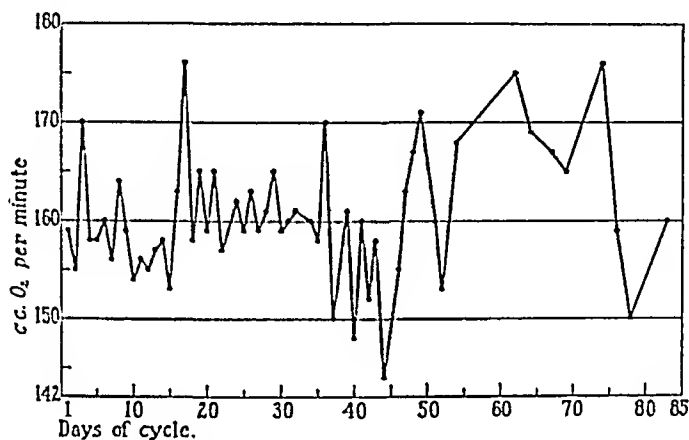


Fig. 4. MEC, age 46. One long cycle

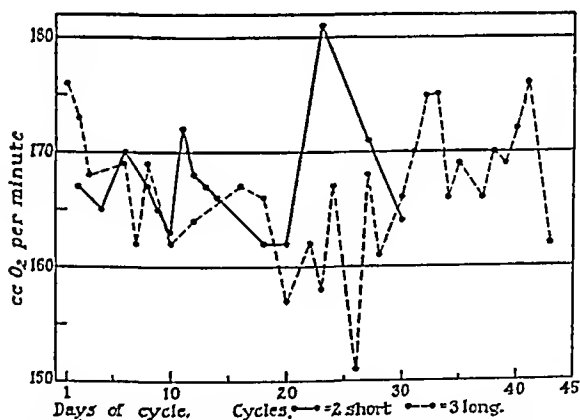


Fig. 5. MEC, age 47. Composite graphs of 2 short and 3 long cycles

At age 48 in the first subject estrin medication was begun at various dosage levels. Oil theelin 500  $\mu$  daily, intramuscularly, raised the BMR from 160 cc.  $O_2$  to 170 cc. A single injection of 2000  $\mu$  raised the BMR to 167 cc. Oil theelin 750  $\mu$  daily, orally, first raised the BMR to 190 cc. and then led to a fall to 162 cc. The potency of injected theelin is therefore roughly double that of orally administered theelin; and doses above the optimal level lower BMR instead of raising it. Other estrogenic preparations (amniotin, ovex, theelol)



given orally each day for a week or more at dosage levels of 500 to 2500 IU raised BMR to 170 to 174 cc., at 1000 IU, but lowered BMR in larger doses. No definite cyclic pattern was seen during the single long cycle occurring that year.

Evidences of endocrine imbalance observed in the first subject were weight loss along with falling BMR, softening of the teeth at 46 to 48, low hemoglobin (50-70% as compared with a usual 82%), hot flashes, great fatigue and extreme nervousness.

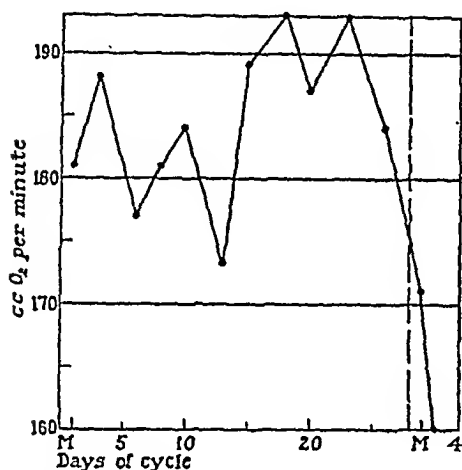


Fig. 6. EMR, age 46. One cycle, BMR

A few observations were made on hot flashes. In several instances hot flashes occurred during a basal metabolism test. They were characterized by much deeper and faster inspirations than usual, together with incomplete expirations. The BMR rose during hot flashes 5 to 15 per cent, presumably because of a faster heart beat and stiffening of the muscles. Observations were also made on several subjects as to the change in skin temperature during

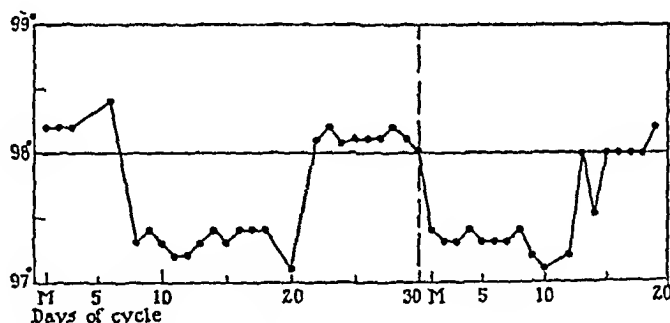


Fig. 7. EMR, age 47. Basal temperatures (mouth) through 2 cycles

hot flashes. One terminal of a thermo-couple was placed in a Thermos-flask at 30°C., and the other (on the base of a ventilated bakelite cup) was placed on the skin of the cheek at the beginning of a hot flash and kept in position until the skin temperature had fallen to a stable level.<sup>2</sup> The temperature increases varied from .5° and 2°C., an amazing rise but entirely reasonable when the normal difference between skin and blood temperature is considered. Although the low estrin dosage begun at age 48 in the first subject was sufficient to lessen the hot flashes in number and intensity, it was not enough to raise the BMR to normal level; moreover larger doses made the hot flashes worse. This resembles the effect of estrin previously reported in ovariectomized women (8, 9).

<sup>2</sup> This apparatus was bought from a research grant from the Council on Pharmacy and Therapy of the A.M.A.

## DISCUSSION

A fall in BMR during the menopause is to be expected along with an increase in weight, both due to lessened thyroid activity. This occurred in the first subject between the ages of 43 to 45. But the sharper fall in BMR at age 46, accompanied by *weight loss*, implies a second factor, perhaps an increase in the ketogenic hormone. Alvarez *et al.* (7) and Ascheim (6) report that most women at the menopause show only the standard drop in BMR, but that some of them are more than plus or minus 10 per cent. Alvarez found 5 of 40 women studied more than 10 per cent below standard. Our first subject evidently falls within this group. The great fatigue experienced at the menopause may well have been due to low BMR.

The cyclic pattern of BMR in young women is usually explained as due to the secretion of estrin early in the cycle and of progesterin toward the end of the cycle, producing two high areas. The absence of these secretions is thought to produce the two low points, at the menstrual period and at ovulation. Certainly it is true that in ovariectomized women moderate doses of estrin produce a rise in BMR (8, 9), although we have as yet no evidence as to the effect of progesterin in such subjects. It is known that as the ovary begins to fail there is a lasting increase in the secretion of the follicle-stimulating hormone. Such an increase would account for the irregularity observed in the first high area in both our subjects. The softening of the teeth observed in our first subject during three years of the menopause, but not before or after, may perhaps be due to a temporary increase of the parathyroid secretion.

In view of the difficulty of getting a long series of BMR tests on several subjects sufficient to establish the usual cyclic pattern at various ages, it might be worth while to use the basal temperature. This worked satisfactorily with our second subject and has been widely used in establishing the day of ovulation.

## SUMMARY

The BMR tests covering 30 cycles were made on one subject at ages 35 (previously reported), 45, 46, 47, 48, together with 18 tests at age 60. The average BMR showed more than the expected fall at the menopause, being -12 to -18 per cent by the Harris-Benedict standard. The greatest drop in BMR coincided with a sharp loss in weight. Weight loss was checked by light estrin-medication. At age 35 the cyclic BMR pattern showed two low points marking the menstrual period and ovulation, and two high areas presumably marking periods of estrin and progesterin secretion. This pattern was again evident at age 45 although the progesterin period was shorter. At age 46 and 47 both estrin and progesterin periods became irregular, and finally only an estrin period appeared.

BMR and basal temperatures were observed in a second subject at ages

46 to 47 over three cycles. The average BMR was  $-5$  per cent H-B. The cyclic pattern showed only a delayed and irregular estrin period.

In the first subject small doses of estrin raised the BMR slightly and reduced the hot flashes, but larger doses depressed the BMR and increased the hot flashes. The effect of hot flashes on breathing, BMR, and skin temperature was observed. Changes in cycle length observed in two subjects followed similar courses. The cycles shortened, then became irregular with increasingly long cycles, and finally stopped rather abruptly. A temporary softening of the teeth was observed in one subject.

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## Relation of Rate of Gastric Evacuation to Time of Onset of Gastric Hunger Contractions

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IT IS GENERALLY ASSUMED on *a priori* grounds (1) that the faster the stomach empties a meal, the earlier hunger contractions occur after the meal. One aspect of this assumption has been established, namely, that the longer one fasts up to 72 hours the more rapidly the stomach empties a standard meal (2). This is explained as due to the greater tone of the musculature of the stomach in hunger, which increases the pressure gradient from the stomach to the duodenum and hence the rate of gastric evacuation. It is clear that 15 to 20 minutes after eating, a 'tonus rhythm' or a series of contractions of small amplitude (digestive peristalsis) begins to occur in the stomach. As gastric evacuation progresses these contractions gradually become greater in amplitude. When the stomach becomes practically empty, these contractions become still more intense and are felt as hunger pain or hunger distress. In most vigorous young men, the first gnawing, slightly burning, or intermittent or continuous pressure pain of fasting may occur when the stomach still contains traces of food (3). For this and other analagous reasons, it has been assumed that the faster the stomach empties, the faster the onset of hunger contractions.

This assumption, however, has never been examined by an experiment in which no other known variable is present other than the rate of gastric evacuation.

### RATIONALE OF METHOD USED

In order to attain the desired end it was, *first*, necessary to use subjects under controlled conditions of previous diet and physical and mental activity. This could be rather easily done.

*Second*, it was necessary to use a standard meal which could be varied only in relation to its consistency, since liquids are thought to be more readily evacuated from the stomach than mushes. Stiff oatmeal mush was used to serve as such a meal. It could be ingested as a stiff paste or as a liquid when liquefied with the enzyme, malt amylase. This yielded a standard meal which

was isocaloric and of the same composition, except when liquefied it contained predominantly dextrans rather than cooked starches.

*Third*, it was necessary to demonstrate that the liquefaction of the cereal meal facilitated gastric emptying or reduced emptying time.

*Fourth*, it was necessary to ascertain if hunger contractions occurred sooner after taking the liquefied cereal than the non-liquefied cereal.

TABLE 1. EFFECT OF LIQUEFYING A CEREAL MEAL WITH MALT AMYLASE ON THE RATE OF GASTRIC EVACUATION

SUBJECT	MEAL COOKED	AREA OF STOMACH			% DECREASE IN AREA		% DECREASE DUE TO AMYLASE
		Immed. after meal	2 hrs. after		Without amylase	With amylase	
			Without amylase	With amylase			
		<i>sq. cm.</i>	<i>sq. cm.</i>	<i>sq. cm.</i>			
R.B.	Farina	30.38	11.72	10.28	61	66	5
H.G.		25.02	10.32	5.62	59	77	19
W.B.		25.15	10.43	7.99	59	68	10
D.D.		20.97	7.21	3.27	66	85	19
J.G.		24.52	8.77	4.22	64	83	19
C.C.	Rolled oats	27.00	10.50	5.05	61	81	20
D.M.		24.51	6.84	6.07	72	75	3
D.M.		26.62	12.59	3.66	53	85	32
J.S.	Cream of wheat	27.10	6.39	3.32	76	88	12
V.J.		20.93	1.59	0	93	100	7
		25.22	8.6	4.9	66	81	15

One part of cereal by dry weight was mixed with 9 parts of water and boiled for 15 min. 100 gm. of barium sulfate was added to 500 gm. of cereal mixture. 500 cc. was ingested and x-ray film made at 1.5, 2, and 2.5 hours. Ovaltine (12.5 gm.) was used as the source of malt amylase.

## EXPERIMENTAL

### EXPERIMENT I. *Effect of the Consistency of a Meal upon its Rate of Evacuation from the Stomach*

Previous studies (4) had shown that the rate of evacuation of a farina test meal from the stomach of dogs and man was significantly more rapid when the meal had been liquefied by treatment with malt amylase than when it was administered in the untreated pasty form.

Further data on this matter, previously unpublished, are available, showing that the increased rapidity of gastric emptying produced by liquefaction of a cereal meal with malt amylase also occurs in human subjects. These data, presented in table 1, show that in every subject tested the percentage decrease in the size of the gastric shadow two hours after ingestion of the cereal test meals was greater when the meal had been liquefied with malt amylase before administration than in the control tests without amylase.

These findings show clearly that the consistency of a meal influences its rate of evacuation from the stomach; a stiff paste being more slowly evacuated than a test meal of the same constituents which has been liquefied by amylolytic action. This provides a means of altering the rate of evacuation of a meal of standard volume and caloric value so that the influence of rate of evacuation on the time of onset of hunger contractions can be studied without varying other factors.

## EXPERIMENT II. *Effect of Liquefying an Oatmeal Test-Meal on the Time of Onset of Hunger Contractions in Dog and Man*

*Method.* Three mongrel dogs were fed daily 30 grams per kilogram body weight of a mixture consisting of 200 cc. of milk and 200 grams of commercial dog food (Pard, Swift). To each dog's portion, 50 cc. of meat juice and one teaspoonful of dried brewer's yeast was added.

TABLE 2. SERIES I. MEAN TIME OF ONSET OF HUNGER CONTRACTIONS AFTER AN OATMEAL TEST WITH ACTIVE AND INACTIVATED MALT AMYLASE  
*Onset times are expressed in minutes after ingestion of test meal*

SUBJECT	NO. OF TESTS	INACTIVATED AMYLASE		ACTIVE AMYLASE		DIFFERENCE OF MEANS		t VALUE OF DIFF. OF MEANS	
		Mean onset time, min.	No. of Tests	Mean onset time, min.					
Dog 1.....	13	188	15	129		59		3.17 <sup>4</sup>	
Dog 2.....	9	203	10	137		66		3.63 <sup>4</sup>	
Dog 3.....	12	118	12	98		20		1.40	
		First H.C. <sup>1</sup>	Second H.C. <sup>1</sup>	First H.C.	Second H.C.	First H.C.	Second H.C.	First H.C.	Second H.C.
Man 1.....	12	134	223	102	176	32	74	2.6 <sup>3</sup>	3.90 <sup>3</sup>
Man 2.....	8	105	180	102	178	3	2	0.75	0.13

<sup>1</sup> First H.C., first set of hunger contractions. <sup>2</sup> Second H.C., second set of hunger contractions. <sup>3</sup> Statistically significant,  $P < 0.05$ . <sup>4</sup> Statistically highly significant,  $P < 0.01$ .  
t values not starred, statistically not significant,  $P > 0.05$ .

Two days per week, the dog to be tested was fed a test meal of 32 grams of oatmeal to which was added 400 cc. of boiling water. After cooking sufficiently to convert the oatmeal into a paste, the oatmeal was cooled to 37°C. One gram of malt diastase was added to the oatmeal and allowed to act on the oatmeal for 30 minutes at 37°C. On alternate test days, the malt diastase was inactivated by boiling for 15 minutes, then added to the oatmeal.

In this same series of experiments, two human subjects after eating a light standard meal fasted for 12 hours, and then were fed the same diet of active malt diastase and oatmeal. Likewise, on alternate test days, the malt diastase was inactivated before being added to the oatmeal. Kymograph tracings were taken by means of the balloon and manometer technique, in the case of dogs by the water manometer; in human beings, by the bromoform manometer. The dogs were trained to swallow the balloon without discomfort and to lie quietly, without restraint, on the table during the course of the experiment. A complete record of gastric activity was made as soon as possible after feeding and continued during the entire course of the experiment. In the case of dogs, each experiment was terminated after the initial hunger activity; in the human subjects, the hunger contractions were recorded

through the first group of hunger contractions, the rest period, and the beginning of the second group of hunger contractions.

*Results.* Examination of the data in table 2 reveals that in 2 of the 3 dogs and in 1 of the 2 human subjects, the onset of hunger contractions was significantly earlier after the test meal containing active amylase than after the one containing inactivated amylase. In the remaining dog and the remaining human subject the differences were in the same direction but were not statistically significant.

TABLE 3. SERIES II. MEAN TIME OF ONSET OF HUNGER CONTRACTIONS AFTER AN OATMEAL AND MILK TEST MEAL WITH AND WITHOUT OVALTINE

*Onset times are expressed in minutes after ingestion of test meal*

SUBJECT	WITHOUT OVALTINE		WITH OVALTINE			DIFFERENCE OF MEANS		t VALUE OF DIFF. OF MEANS		
	No. of tests	Mean onset time, min.	No. of tests	Mean onset time, min.						
Dog 1. ....	7	185	6	165		20		0.28		
Dog 3. ....	9	228	8	230		2		0.11		
		First H.C.	Second H.C.		First H.C.	Second H.C.	First H.C.	Second H.C.	First H.C.	Second H.C.
Man 1. ....	9	134	201	9	128	184	6	17	0.42	1.19

See footnote to table 2.

EXPERIMENT III. *Effect of Adding Malt Amylase to a Mixed Meal on the Time of Onset of Hunger Contractions in Dog and Man*

*Method.* The mixed meal used consisted of oatmeal and milk. The dogs were fed the same daily diet of 'Pard', milk, meat juice and brewer's yeast. On test days each dog was fed 15 grams of a commercial product containing malt diastase (Ovaltine), 32 grams of oatmeal, 300 cc. of water and 250 cc. of milk. On alternate test days Ovaltine was not added to the diet. The human subject fasted for 12 hours before the test was made and then was fed the same test diet of Ovaltine, oatmeal, water and milk, while on alternate test days the Ovaltine was not added to the diet. After the oatmeal was cooked, the milk was added and the mixture was cooled to 37°C. before the Ovaltine was added. The Ovaltine was allowed to act on the oatmeal and milk for 30 minutes at 37°C.

*Results.* Table 3 gives the results of this series of experiments with a test meal of milk and oatmeal with and without malt amylase. In neither the two dogs nor the human subject did the addition of malt amylase to the test meal cause a significant change in the mean time of onset of hunger contractions after the test meal.

*Differentiation between Digestive Peristalsis or a 'Tonus Rhythm' and the First Hunger Contractions*

In both series of experiments the tracings showed gastric tonus activity shortly after feeding. The tonus either maintained its level as recorded in the

first few minutes of the experiment or else increased gradually. In the dogs the tonus rhythm gradually developed into *Type I* hunger contractions. However, in *dog 2* the change from gastric tonus rhythm to hunger contractions was so gradual that a point of demarcation between tonus and hunger activity was very difficult to determine. In this dog the onset of hunger contractions was arbitrarily designated as that time at which a 0.5 inch rise in mean intra-gastric pressure had occurred. In *dogs 3* and *5* the point of demarcation between tonus rhythm and hunger contractions was easily determined.

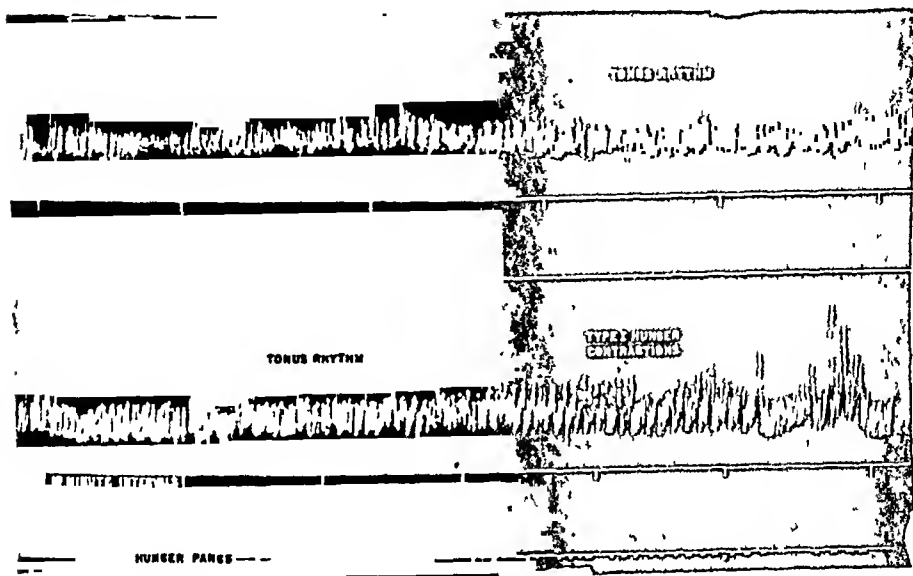


Fig. 1. KYMOGRAPHIC TRACING of gastric motility showing onset of hunger contractions and correlation of hunger pangs with hunger contractions in a human subject

In man the tonus rhythm of the stomach changed abruptly into *Type I* hunger contractions (fig. 1). In both subjects the tonus rhythm aroused no hunger sensations but every *Type I* hunger contraction was felt as a definite hunger pang which corresponded directly with the hunger contractions recorded on the tracing. The basal tonus pressure in all tests on human subjects remained constant throughout each experiment.

#### DISCUSSION

Since it has been demonstrated that liquefaction of a pasty meal by malt amylase causes it to leave the stomach more rapidly, it is reasonable to conclude that the earlier onset of hunger contractions when the liquefied meal is fed is related to its more rapid evacuation from the stomach. The only other factor which must be taken into account is the difference in the state of the starch molecules in the two meals. In the meal without amylase, cooked starch is present whereas in the amylase-treated meal, much of the starch has been



broken down to dextrins and smaller particles. This might accelerate the rate of absorption of the digested starch.

It is possible that accelerated absorption of the starch would influence the time of onset of the hunger contractions by causing the blood sugar to return to basal levels at an earlier time. However, studies on the relationship between spontaneous fluctuations in blood sugar level and the occurrence of gastric hunger contractions have failed to reveal any synchrony (5, 6, 7). Therefore we interpret the earlier onset of hunger contractions with the liquefied meal as being due to the stimulus of an empty stomach.

Elsewhere (8) we have presented an analysis of the factors contributing to hunger and appetite. The present study provides evidence regarding one of these factors, namely, the influence of the state of fulness of the stomach upon the onset of hunger contractions. It has been well known for some time that the filling of the stomach with substances having no caloric value can temporarily inhibit gastric hunger contractions. While the present study indicates that the state of fulness of the stomach influences hunger, it should be pointed out that this is only one of many factors operating to control hunger and that in the presence of stronger influences it might not have any significant effect.

Malt amylase speeds gastric evacuation when a plain oatmeal test meal is used, but it does not do so in the case of a mixed meal such as oatmeal and milk. Since amylase does not speed the evacuation of this type of meal it is not surprising to find that it does not influence the time of onset of hunger contractions.

#### SUMMARY

Liquefaction of a cereal meal by malt amylase causes it to leave the stomach more rapidly in both man and dogs. Associated with this augmented evacuation rate there is a shortening of the time between the ingestion of the test meal and the appearance of hunger contractions in both man and dogs. A mixed meal (cereal plus milk) does not evacuate more rapidly when treated with amylase nor does treatment with amylase significantly affect the time of onset of hunger contractions.

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# *Role of Blood Sugar Levels in Spontaneous and Insulin-Induced Hunger in Man*

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THE HUNGER SENSATIONS which accompany deprivation of food in man are complex in nature including as they do weakness, fatigue, irritability, headache, nausea, diffuse feeling of emptiness and hollowness, the sensations which accompany sweating and trembling as well as the epigastric pang.

Recent study in this laboratory of the effect of vagotomy on insulin-induced hunger indicates that bilateral interruption of the vagus nerves abolishes the gastric contractions and the resulting epigastric pang but the remainder of the sensation complex is experienced as in the intact individual (1). This holds true also for spontaneous hunger sensations following bilateral vagotomy, bilateral dorsolumbar sympathectomy or anatomically verified transection of the spinal cord in the neck or high in the thorax (2). These studies have led us to believe that the gastric 'hunger' contractions and the associated epigastric pang are but one and a dispensable component of the entire complex of hunger sensations.

Because previous studies (3-5) on the rôle of blood sugar in hunger have been concerned almost entirely with the relationship of blood sugar to gastric contractions and the resulting epigastric sensation we have investigated the rôle of blood sugar in the entire complex of spontaneous and insulin-induced hunger sensations.

## METHODS

Five adult normal females who had volunteered in connection with other studies in carbohydrate metabolism were employed. All observations were made after 18 hours of fasting, in an air-conditioned, sound-proof room, with the subjects reclining comfortably.

Three series of observations were made on each subject, on separate occasions, usually at intervals of from 2 to 5 days. In the first series venous blood was obtained for glucose determinations at intervals of 20 minutes for 80 minutes in the post-absorptive state. In the second, 0.3 gm. of glucose per kilogram of body weight was administered intravenously, and blood specimens

drawn as before. In the third, 0.1 unit of insulin per kilogram of body weight was administered intravenously, and blood specimens obtained as before. The subjects were in ignorance of the materials being administered. Without the use of leading questions they were asked to describe in detail all the sensations they experienced.

Blood glucose was determined by the Folin modification of the Folin-Wu method (6).

TABLE 1. RELATIONSHIP OF BLOOD SUGAR TO HUNGER SENSATIONS. TIMES ARE MEASURED FROM TIME OF INSULIN INJECTIONS

SUBJECT	DOSE OF INSULIN	BASAL BLOOD SUGAR	LOWEST BLOOD SUGAR	TIME OF LOWEST BLOOD SUGAR	BLOOD SUGAR AT ONSET OF HUNGER	TIME OF ONSET OF HUNGER	DURATION OF HUNGER	BLOOD SUGAR AT END OF ACUTE HUNGER
	units	mg. %	mg. %	min.	mg. %	min.	mg. %	mg. %
S.A.....	6.3	82	31	25	40	40	20	58
H.C.....	5.0	82	24	20	43	48	12	59
G.H.....	5.9	71	34	23	39	47	13	54
R.R.....	6.1	76	42	20	42	36	29	58
D.H.....	5.8	85	41	20	50	43	13	72

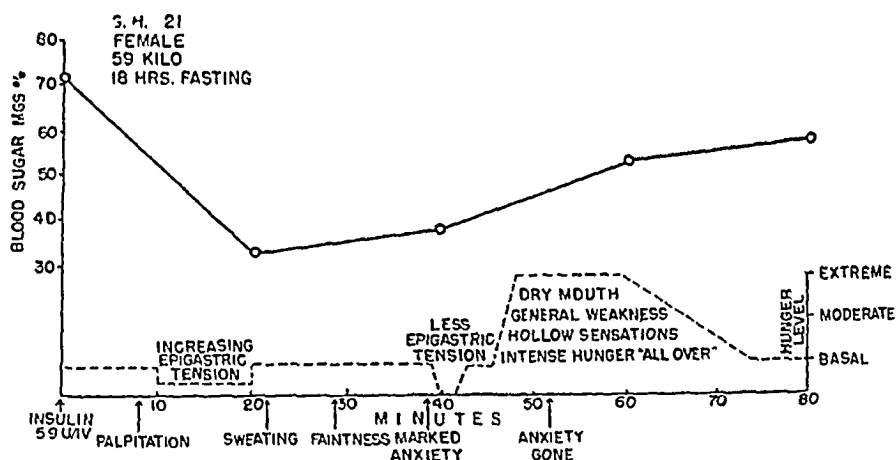


Fig. 1. RELATIONSHIP of blood sugar and hunger sensation in subject G.H. Time is in minutes after insulin injection. Solid line represents blood sugar; interrupted line represents hunger on an arbitrary scale of intensity.

## RESULTS

In the first series of observations, the fluctuations of spontaneous hunger sensations bore no relationship to the essentially minor variations in fasting blood sugar level in all subjects. The initial blood sugar levels ranged from 71 to 89 mg. per cent; the maximum variation for each individual ranged from 4 to 9 mg. per cent.

In the second series of observations, the intravenous injection of from 15 to 18.9 gm. of glucose and the resulting hyperglycemia which lasted from 40 to

60 minutes had no effect on basal hunger sensations in any subject. The initial blood sugar levels, in this series, ranged from 77 to 99 mg. per cent; the maximum level for each individual varied from 143 to 210 mg. per cent.

In the third series of observations, the intravenous injection of from 5.0 to 6.3 units of regular insulin reproduced the complete pattern of spontaneously occurring hunger in all subjects. This is tabulated in table 1, and illustrated for one subject in figure 1. On the average the insulin-induced hunger occurred 42 minutes, 27 minutes after the lowest blood sugar, at a time when the blood glucose was 42 mg. per cent, and subsided at a time when this was 61 mg. per cent, which was below the fasting levels in all cases.

### DISCUSSION

The manner in which blood sugar acts is somewhat analagous to the rôle of arterial oxygen content in respiratory control, where, under normal circumstances, the oxygen content of the blood has no determining rôle, but under abnormal circumstances hypoxemia may stimulate the chemo-receptors of the carotid and aortic bodies. In the case of hunger the location of the cells sensitive to glucose lack is completely unknown, as is the nature of the stimuli, which may be of a nervous or humoral kind. Insulin, per se, is not involved, since the inhibition of the hypoglycemic response to insulin by supplementary glucose will abolish both the extragastric sensations and those associated with increased gastric motility (3, 4).

These findings are consistent with the failure of parenteral administration of glucose prior to feeding to inhibit food intake in both the dog and rat (7, 8).

### SUMMARY

The fluctuations in blood sugar levels which occur spontaneously in fasting human subjects are small and cannot be correlated with the spontaneously occurring phases of hunger sensations. Hyperglycemia produced by intravenous injection of glucose has no detectable effect upon these spontaneously occurring hunger sensations. When abnormal hypoglycemia is induced by insulin injection, hunger sensations are evoked. These begin after the blood sugar level has begun to rise from its nadir and subside before the normal blood sugar level is attained.

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# *Pupil Size in Ametropia*

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IT IS A COMMON ASSUMPTION that the pupil of the myope is larger and that of the hyperope smaller than the pupil of the emmetrope. Duke-Elder (1) states, "On the average it [the pupil] is wider in the short-sighted than the long. . . ." Zoethout (2) writes, "Most authorities state that in the myope the pupil is larger and in the hyperope smaller than in the emmetrope; others deny this. Tscherning says that as a rule it is larger in the myope, 'at least in appearance, for the anterior chamber of myopes is often deeper which makes the pupil appear larger.'" It is the purpose of the present study to determine a) whether or not there is any relationship between refractive state and pupil size and b) whether or not the relationship is present only when apparent pupil size is considered as Tscherning implies.

## METHODS

At the time of the administration of the physical examination to male students entering Stanford University one of the authors estimated the refractive state by means of a retinoscope and trial lenses; while an associate estimated the pupil diameter.<sup>1</sup> The refractive state in the two major meridians was determined and the average (equivalent sphere) used as a measure of ametropia. The pupil diameter was determined by the use of a rule having a series of half circles varying in size by one-half millimeter steps from 3 mm. to 8 mm. During this determination the subject faced a uniformly illuminated white sheet behind the examiner's head. The measurements made on 266 students (532 eyes) comprise the basic data for the study.

## RESULTS

The information desired is most simply expressed by the coefficient of correlation between the refractive state and the pupil diameter. This was found to be  $-0.243$ , the negative sign indicating association between hyperopia and small pupil or myopia and large pupil. The probability that a coefficient as large as this could have occurred by chance is less than 1 in 1000. The regression formula is  $Y = 4.7908 - 0.0883 X$ , where  $Y$  is the pupil diameter in

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<sup>1</sup> The authors express appreciation to Dr. Edwin B. Mehr, optometrist, who made the pupil measurements.

millimeters and  $X$  is the refractive state in diopters. From the formula it may readily be determined that the average pupil size for an emmetrope is 4.79 mm., for a 5 D myope, 5.23 mm., and for a 5 D hyperope, 4.35 mm.

Clearly, there is a relationship between refractive state and apparent pupil size which differs significantly from zero. The coefficient of correlation is, however, small and, hence, of little predictive value. It may be stated that approximately 6 per cent (correlation coefficient squared) of the variability in pupil size is associated with variability in refractive state.

The apparent pupil size is larger than the real pupil size, the amount depending upon *a*) the corneal power and *b*) the depth of the anterior chamber. Myopia is associated with a greater corneal power and a larger chamber depth (3)<sup>2</sup>, both factors resulting in a larger apparent size. The chamber depth and corneal curvature were not measured on the subjects in the present study; however, it was possible to obtain from Stenström's data regression coefficients which yielded corneal powers and anterior chamber depths for the various refractive states. Using these calculated values, average real pupil sizes could be computed.

The coefficient of correlation between real pupil size and refractive state was considerably lower than that for apparent pupil size and refractive state, being  $-0.104$ . This coefficient does, however, reach the 2 per cent level of significance. The regression coefficient in this case is  $Y = 4.2288 - .0303 X$ , where  $Y$  is real pupil size in millimeters and  $X$  is refractive state. Thus, the average real pupil size for emmetropia was 4.23 mm., while for a 5 D myope it was 4.38 mm., and for a 5 D hyperope, 4.08 mm. The correlation coefficient may be interpreted as indicating that approximately one per cent of the variability in real pupil size is associated with variability in ametropia.

#### SUMMARY

There seems to be real basis for the statement that pupil size varies with type and degree of ametropia, the myope having the larger pupil. Due, however, to the great variability in pupil size for any given refractive state, the correlation coefficient is low and little can be done in the way of prediction. Tscherning suggested that the difference in pupil size between myopes and hyperopes might be due to the greater magnification in the former case. This view is supported by the present finding that while 6 per cent of the variability in apparent pupil size is associated with refractive state, only about one per cent of the variability in real pupil size is so associated. The relationship between real pupil size and refractive state, while very slight, probably rests upon differences in the stimulus to accommodation. Unfortunately, this

<sup>2</sup>The correlation coefficients found by Stenström were  $-0.18$  between refractive state and corneal power;  $-0.34$  between refractive state and chamber depth.

factor was not controlled in the present experiment. All subjects fixated an object at about 50 cm., and since no correction lenses were worn, the hyperopic subjects accommodated a greater amount than did the myopic subjects. It is surprising that under these conditions so little relationship between real pupil size and refractive state was found. If accommodation is controlled it may even be found that the real size of the pupil is larger for the hyperope than for the myope. Further study in which pupil size is measured with *a*) accommodation relaxed and *b*) all subjects fixating an object at a given distance should reveal whether or not the slight degree of relationship obtained is in fact due to differences in accommodation. It seems safe, however, at present to conclude that relationship does exist between apparent pupil size and refractive state and that such relationship for the most part depends upon chamber depth and corneal power differences for the various refractive states. When correction is made for these factors and real pupil size calculated, the remaining relationship is very slight. It is so slight, in fact, that if accommodation is carefully controlled the correlation coefficient might prove to be zero or even exhibit a reversal of sign.

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# *Venous Pressure in the Saphenous Vein at the Ankle in Man during Exercise and Changes in Posture<sup>1</sup>*

ALBERT A. POLLACK<sup>2</sup> AND EARL H. WOOD. *With the technical assistance of ROY ENGSTROM From the Section on Physiology, Mayo Foundation, Rochester, Minnesota*

THE PURPOSE of this investigation was to study the effect of walking and the position of the body on the venous pressure in the legs of normal male subjects.

Smirk (1) in 1936 reported the first direct measurement of venous pressure at the ankle during walking in one normal subject. Beecher, Field and Krogh (2) in the same year reported on the indirect measurement of the venous pressure in the human leg during walking. Others (3-7) have reported the effects of different muscle actions on the venous pressure in the leg by both direct and indirect methods. Recently Pollack and Wood (8) and Henry (9) gave preliminary reports of direct venous pressure studies in the human leg during walking.

## MATERIALS AND METHODS

The manometer used in these studies was a resistance wire, strain gauge manometer<sup>3</sup> similar to that described by Lambert and Wood (10). The pressure variations were recorded on a kymographic camera (11).

The manometer system and wash bottle were filled with air-free 0.9 per cent solution of sodium chloride containing 10 mg. sodium heparin per 500 cc. of solution. The electrocardiogram was recorded from two lead electrodes placed 5 cm. below the respective nipples. The R-wave of the electrocardiogram activated an instantaneous heart rate indicator (12).

The subject's legs were shaved from the knee down and a U-shaped aluminum frame with two rigid prongs at the base was taped to the lateral surface of each leg just above the lateral malleolus. Two similar rigid prongs were attached to each strain gauge manometer, and then by means of four double-ended universal clamps the manometers were attached to the aluminum supports on the legs (fig. 1).

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<sup>1</sup> Abridgment of thesis submitted by Dr. Pollack to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

<sup>2</sup> Fellow in Medicine.

<sup>3</sup> Model P6-4D-250, manufactured by the Statham Laboratories, 9328 Santa Monica Blvd. Beverly Hills, Calif.



A 15-cm. length of flexible polythene tubing<sup>4</sup> with an outside and inside diameter of 0.97 mm. and 0.58 mm., respectively, was used as a venous catheter. This tubing passes easily through a no. 17 hypodermic needle. The venous catheter was attached to a 25-cm. length of polythene tubing (O.D. 2.8 mm., I.D. 2 mm.) by means of a blunt-tipped no. 24 hypodermic needle. This larger-sized polythene tubing was attached directly to the manometer. Strain gauge manometers with a range of  $\pm 4$  p.s.i. (P6-4D-250) were used at the ankles in these experiments. The manometer system was overdamped so that 0.20 second was required for the manometer system to register 95 per cent of the full response to an instantaneous pressure change at the catheter tip.

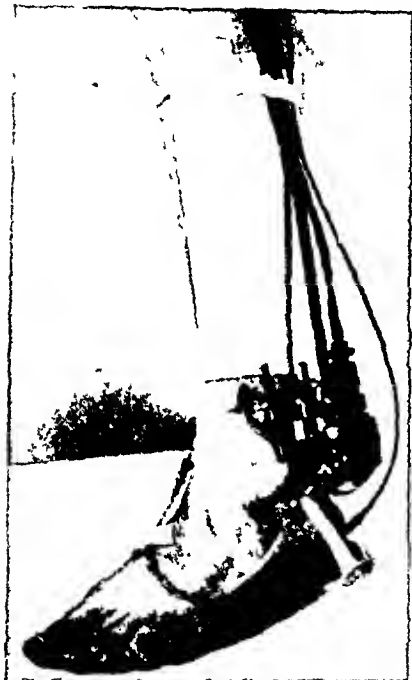


Fig. 1. STRAIN GAUGE MANOMETER attached to ankle and coupled to venous catheter inserted into saphenous vein.

In order to determine the hydrostatic pressure effects on a column of fluid the height of which was approximately equal to the height of the blood column extending from the ankle to the base of the heart and to obtain some control data as to the effects of the accelerative forces induced by walking on the manometer system, a glass reservoir was attached to the subject's chest at about the level of the third thoracic interspace. This was coupled by means of rubber tubing to the polythene tubing and manometer system, identical to the arrangement used for recording of venous pressure in the catheterized leg. The two manom-

eters were adjusted to approximately equal sensitivity by regulation of the voltage supply.

To indicate each time the catheterized foot was lifted and replaced on the floor, a balloon was devised to fit the heel. The pneumatic pressure variations generated in the balloon by each step were recorded by means of a strain gauge manometer (P8-8G-450). Respiration was recorded by means of a thermocouple placed in a plastic nose piece.

A no. 17 hypodermic needle was inserted into the great saphenous vein at the ankle after preliminary infiltration of the area with a 2-per cent solution of procaine hydrochloride. The catheter was passed through the needle into the vein for a distance of about 10 cm. and the needle was withdrawn, leaving the catheter in place. The system was flushed frequently with heparinized

<sup>4</sup> Manufactured by Surprenant Electrical Insulation Co., 199 Washington St., Boston 7, Mass.

physiologic saline solution in order to prevent clotting of blood in the catheter. It was found that cutting a small lateral opening into the lumen of the catheter 1 or 2 mm. from the tip practically eliminated obstruction of the catheter due to clot formation. Simultaneous continuous recordings were made of the venous pressure, respiratory rate, heart rate and electrocardiogram while the subject was supine, sitting, standing still, standing on the toes, taking single steps and during walking on a horizontal treadmill at 1.7, 2.6 and 3.3 miles per hour. In a few studies, recordings were also obtained while the subjects walked on the treadmill inclined upward to approximately  $20^\circ$ .

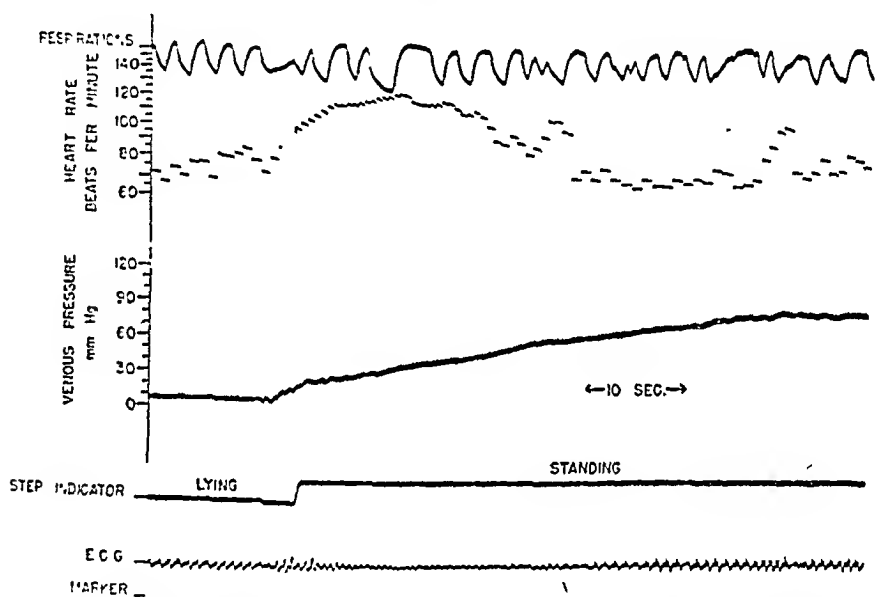


Fig. 2. EFFECT OF ARISING from supine to standing position on venous pressure at the ankle.

Manometers were calibrated against a mercury manometer and zero pressure base lines were recorded at the level of the catheter tip in each position assumed by the patient. The tip of the catheter was immersed in a column of fluid in a 1 cm. I.D. tube held at the zero point for the various base lines in order to eliminate the factor of capillarity of the catheter.

#### RESULTS

The venous pressure at the ankle was measured in the supine, sitting and quiet standing positions in 11 normal subjects. The average<sup>6</sup> venous pressure at the ankle in the supine position was 11.7 mm. Hg with a range of from 7 to 16 mm. Hg pressure (fig. 2). The range of stabilized venous pressure at the ankle in the sitting position was from 45 to 67.5 mm. Hg with an average of 56.0 mm.

<sup>6</sup> Average of the average values for each subject.

Hg. The difference between the stable venous pressure in the sitting and lying position was 44.3 mm. Hg.

The average venous pressure at the ankle in the quiet standing position was 86.8 mm. with a range of 78.5 to 92.6 mm. Hg. The difference between the average stable sitting and standing venous pressure was 30.8 mm. (table 1). The average time required for the venous pressure to increase to the standing value after the subject arose from the sitting to the standing position was 21.8 seconds (fig. 3).

In 5 of these normal subjects, the calculated hydrostatic pressure of a column of blood from the third interspace to the right of the sternum to the tip

TABLE 1. COMPARISON OF VENOUS PRESSURE AT THE ANKLE IN THE SUPINE, SITTING AND STANDING POSITIONS

SUBJECT	VENOUS PRESSURE, MM. Hg		
	Supine	Sitting	Standing
1	14	56.3	89.4
2	12	57.6	91.5
3	16	45	78.5
4	14	58.1	84.7
5	11.5	47.6	85.8
6	7	57.9	85.5
7	8	62.7	92.6
8	10	55.8	85.6
9	14	67.5	90.3
10	12	56.5	81.5
11	10	50.5	89.3
Average . . . . .	11.7	56.0	86.8

of the venous catheter in the sitting position averaged 60.2 mm. Hg and in the standing position 92.5 mm. Hg. The average venous pressure in the sitting position was 58.8 mm. and in the standing position it was 90.5 mm. The difference between the venous pressure at the ankle in the standing position and the calculated hydrostatic pressure for the same column of blood was 2.0 mm. Hg, while the difference between the venous pressure and the calculated hydrostatic pressure in the sitting position was 1.4 mm. Hg. Thus when the subject was at rest in the sitting or standing position, the venous pressure at the ankle was sufficient to support a column of blood approximately to the level of the third interspace at the sternum. The third interspace at the sternum is described by Cunningham (13) as the level of the middle of the right auricle.

In the same group of 5 subjects, the hydrostatic pressure at the ankle of the fluid column extending from the ankle to the anterior chest wall was 41.4 mm. Hg in the sitting position as compared to the calculated hydrostatic

pressure of 41.0 mm. Hg. In the standing position the pressure in this artificial fluid column was 70.8 mm. Hg as compared to the calculated hydrostatic pressure of 69.8 mm. Hg (table 2).

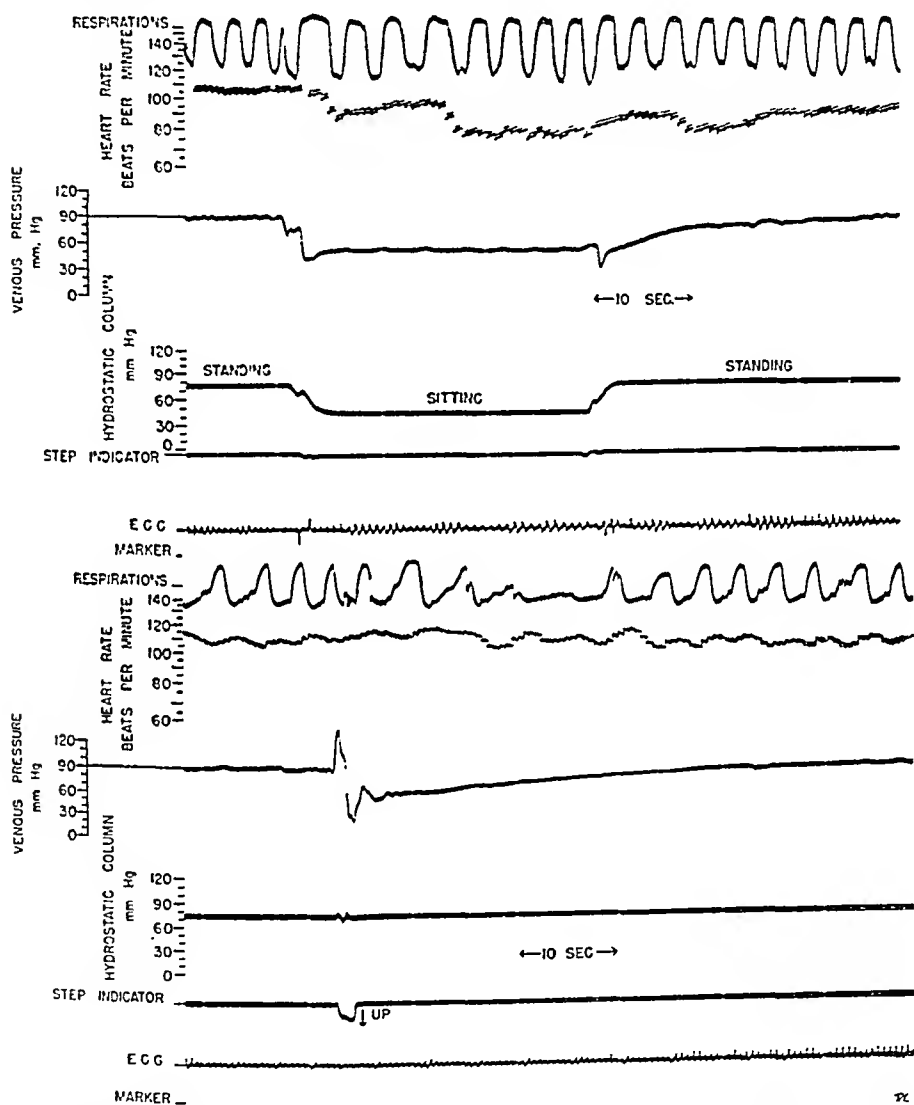


Fig. 3 (upper). EFFECT OF CHANGE from standing to sitting position and back to standing position on venous pressure at the ankle.

Fig. 4 (lower). EFFECT OF A SINGLE STEP on venous pressure at the ankle.

The effect of taking a single step on the venous pressure at the ankle was determined in 10 normal subjects. These subjects took one step forward, after which they resumed their former resting-standing position with both heels together. The changes in venous pressure produced by a single step are

illustrated in figures 4 and 5. Before the heel left the floor there was an average initial decrease in venous pressure of about 0.3 mm. Hg. The lowest point of this fall in pressure was assumed to be the zero time or starting time of the step. The pressure then quickly increased to an average peak of 97 mm. Hg with a range from 81 to 117 mm. in 0.5 second and then started to fall. The heel started to leave the floor 0.7 second after the initial deflection and the pressure decreased to 88 mm. Hg. By the time the heel was completely off the

TABLE 2. COMPARISON OF VENOUS AND HYDROSTATIC PRESSURES AT THE ANKLE IN THE SEATED AND STANDING POSITION

SUBJECT	VENOUS HYDROSTATIC COLUMN (MEASURED AND CALCULATED PRESSURES)			ARTIFICIAL HYDROSTATIC COLUMN (MEASURED AND CALCULATED PRESSURES)		
	Vert. distance 3rd interspace to catheter tip, cm. A	Calculated press., mm. Hg $\frac{A \times 1.06}{13.55}$	Measured venous press., mm. Hg	Vert. distance hydrostatic reservoir to catheter tip, cm. B	Calculated press., mm. Hg $\frac{B}{13.55}$	Measured hydrostatic press., mm. Hg
<i>Standing</i>						
1	112.8	88.2	87.6	103	76	79
2	122	95.4	92.7	84	62	62
4	113.5	88.8	88.8	99	73	73
7	127	99.5	96.6	90	66	66
8	115.8	90.5	86.8	97	72	74
Average...	118.2	92.5	90.5	94.6	69.8	70.8
<i>Sitting</i>						
1	70.2	54.9	55	75.5	56	57
2	78.5	61.4	58	42	31	31
4	77.5	60.6	61.2	57.5	42	42
7	84.7	66.3	64.3	49	36	35
8	74	57.8	55.6	54.5	40	42
Average...	77.0	60.2	58.8	55.7	41.0	41.4

floor, one second after zero time, the venous pressure at the ankle had decreased to 68 mm. Hg and continued to fall until 1.3 seconds on the average to 45 mm. Hg with a range from 30 to 60 mm. Hg. The pressure then began to increase and at 1.6 seconds, when the heel started back toward the floor, it had reached 47 mm. Hg. At 1.7 seconds after the starting time of the step it had reached 68 mm. Hg and then fell again so that 2.1 seconds after zero time, as the heel returned to the floor, the venous pressure was 63 mm. Hg. The lowest venous pressure after the step occurred 2.2 seconds after the heel touched the floor and averaged 46 mm. Hg with a range from 36 to 68 mm. Hg. The standing control level was reached on the average at 22.9 seconds after the heel had returned to the floor.

Normal subjects walked on a level treadmill at speeds of 1.7, 2.6 and 3.3 miles per hour, for periods from 10 to 40 seconds. The typical changes in the venous pressure at the ankle produced by walking are illustrated in figures 6, 7, 8 and 9. After an initial rise at the onset of the first step, the venous pressure at the ankle fell rapidly during the first three steps in every instance. The mean venous pressure decreased to a stable value on the average after 7.5 (4 to 12) steps of the walk had been completed and remained at this value until the treadmill was slowed at the termination of the walk.

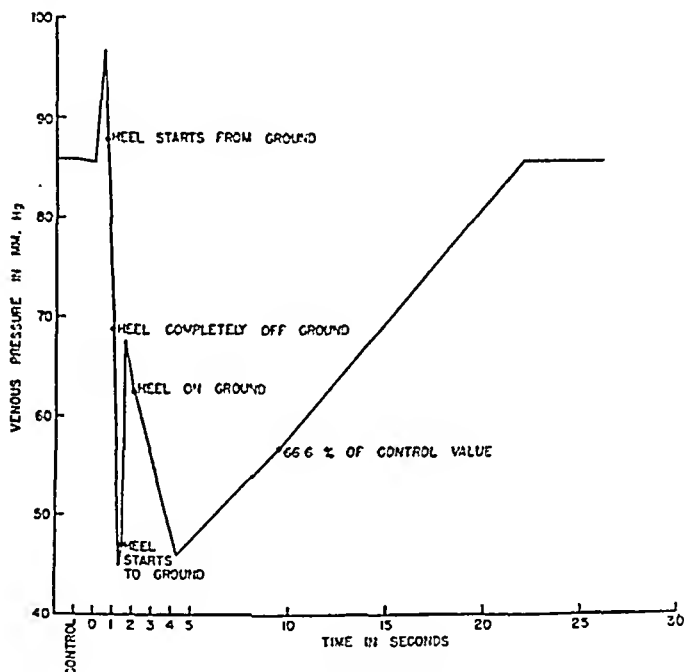


Fig. 5. AVERAGE CHANGES of venous pressure at the ankle produced by a single step (10 subjects).

The average stable value of the mean venous pressure, as determined by a planimeter, at 1.7 miles per hour was 22 mm. Hg with a range from 11 to 31 mm. Hg. At 2.6 miles per hour this value was 24 mm. with a range from 9 to 38 mm. Hg, and at 3.3 miles per hour it was 24 mm. Hg with a range from 10 to 43 mm. (table 3). In this series of determinations the differences in venous pressures during walking at these three speeds were not statistically significant (the  $p$  values were greater than 0.05). After completion of the last step of the walk an average period of 31 (8-57) seconds was required for the venous pressure at the ankle to return to the resting standing control value.

Three normal subjects were walked on an inclined treadmill at different rates of speed. All 3 subjects showed a fall in venous pressure of the same

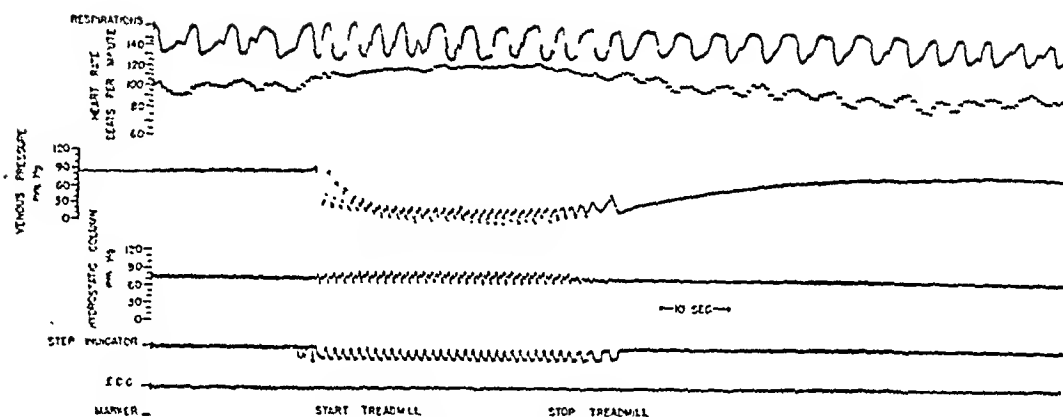


Fig. 6. EFFECT OF WALKING 1.7 miles per hour on venous pressure at the ankle.

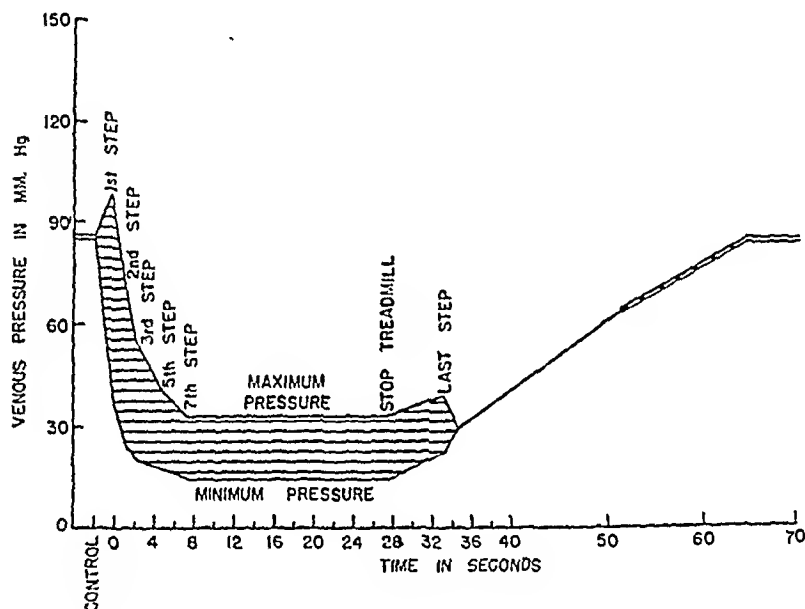


Fig. 7. AVERAGE CHANGES in venous pressure at the ankle produced by walking 1.7 miles per hour (10 subjects).

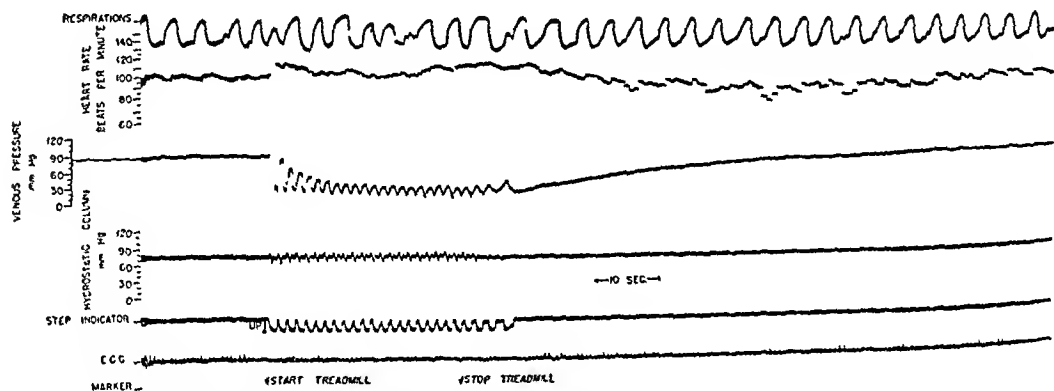


Fig. 8. EFFECT OF WALKING 2.6 miles per hour on venous pressure at the ankle.

degree as the fall that occurred in walking on a level treadmill (table 4). After periods of walking, small pulsations usually appeared in the venous pressure tracings when the pressure was sufficient to support a column of blood to about the lower level of the abdominal cavity. These pulsations in venous

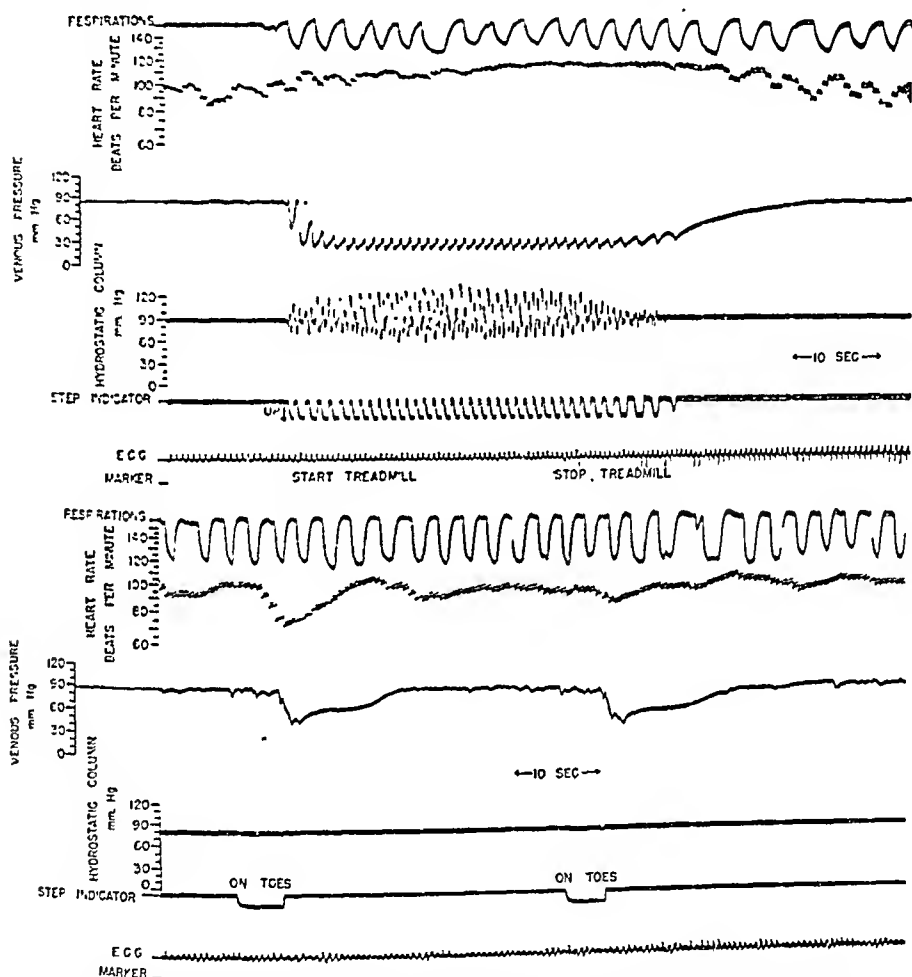


Fig. 9 (upper). EFFECT OF WALKING 3.3 miles per hour on venous pressure at the ankle.

Fig. 10. (lower). EFFECT OF RISING on tiptoe on venous pressure at the ankle.

pressure at the ankle were also seen when the subjects were standing or sitting at rest. Sometimes these pulsations were coincident with respiration, and sometimes they occurred at the same time as the heart beat. There was no drop in the mean pressure of the artificial hydrostatic column during periods of walking (figs. 6, 8 and 9).

The effect on the venous pressure in the leg produced by elevating the body to the tiptoe position by voluntary extension of the ankles was de-



TABLE 3. VENOUS PRESSURE AT THE ANKLE IN NORMAL SUBJECTS DURING QUIET STANDING AND WHILE WALKING AT DIFFERENT RATES OF SPEED (DETERMINED BY PLANIMETRY)

SUBJECT	MEAN VENOUS PRESSURE, MM. Hg			
	Quiet standing	Walking 1.7 m.p.h.	Walking 2.6 m.p.h.	Walking 3.3 m.p.h.
1	89.4	20	29	22
2	91.5	20.5	30	25
3	78.5	20.6		
4	84.7	30.6	26.9	43.2
5	85.8	23.5	38	
6	85.5	25.3	28	32.3
7	86.5	23		
8	84.3	23.5	21.3	21.5
9	90.3	25	13	11
11	89.3	11	8.5	10
Average.....	86.6	22.3	24.3	23.6

TABLE 4. VENOUS PRESSURE AT THE ANKLE DURING QUIET STANDING AND WALKING AT ZERO AND A 20-DEGREE UPWARD INCLINE

SUBJECT	MEAN VENOUS PRESSURE, MM. Hg				
	Quiet standing	Walking 1.7 m.p.h.		Walking 2.6 m.p.h.	
		Level	Incline	Level	Incline
1	89.4	20	25	29	24
2	91.5	20.5	26	30	26
4	84.7	30.6	49	26.9	

TABLE 5. CHANGES IN VENOUS PRESSURE AT THE ANKLE PRODUCED BY RISING ON TOES FROM THE STANDING POSITION

SUBJECT	VENOUS PRESSURE, MM. Hg						TIME IN SECONDS FROM RETURN OF HEEL TO FLOOR TO:	
	Quiet standing	Heel starts from floor	Heel off floor	Heel first touches floor	Heel on floor	Lowest press. after heel on floor	Lowest subsequent press	Return to resting control press
1	87.5	87.5	118	66	112	54	0.9	16
2	93	90	110	103	100	62	2.3	10.4
5	90	103	90	90	82	76	0.5	2.5
7	90	120	93	69	87	67		23
8	85	90.5	87.5	60.5	60	57	0.5	8
9	88	93.5	104.5	83.5	69	60.5	0.6	14
11	86	84	84	74.3	71.8	39	1.5	11.5
Average..	88.5	95.5	98.1	78.0	83.1	59.4	1.0	12.2

terminated in 7 normal subjects. The body weight was supported entirely on the toes when in the tiptoe position and the position of the toes was maintained unchanged during the procedure. The standing control pressure

averaged 89 mm. and ranged from 85 to 93 mm. Hg. The venous pressure increased as the heel started from the floor to an average value of 96 mm. Hg with a range from 84 to 120 mm. This increase continued as the heel was raised entirely off the floor to an average value of 98 mm. with a range from 84 to 118 mm. Hg. The venous pressure then decreased so that when the heel started back to the floor the average value was 11 mm. (range 14-28 mm.) Hg less than the original resting control pressure. When the heel had returned to the floor the pressure averaged 83 mm. Hg with a range from 60 to 112 mm. Hg. The minimal venous pressure occurred at an average time of 1.0 second after the heel had returned to the floor and averaged 59 mm. with a range from 39 to 76 mm. Hg (fig. 10, table 5). On the average 12.2 seconds elapsed from the time the heel returned to the floor until the venous pressure had increased to the previous resting level.

#### COMMENT

It is evident from this investigation that in the resting, sitting or standing position the average venous pressure at the ankle is approximately equal to the hydrostatic pressure exerted by a column of blood extending from the point of measurement to the third thoracic interspace at the sternum.

In taking a single step, the changes in pressure recorded in the artificial hydrostatic column were readily explained by the variations in the height of the column of fluid and the accelerative forces acting in the manometer and fluid systems caused by the motion of the step (fig. 4). The decreases in venous pressure at the ankle associated with exercise cannot be explained on this basis. This is evident in this instance by the decrease in pressure which occurred when the subjects stood on their toes, since the drop in venous pressure at the ankle was not associated with appreciable accelerative forces nor decreases in the vertical distance separating the ankle from the level of the heart (fig. 10).

When one is preparing to elevate the heel in taking a single step, there is contraction of the gastrocnemius and soleus muscles and a resulting application of pressure on the veins of the leg. This produces the rise in venous pressure at the ankle and causes a portion of the blood contained in the veins to flow upward out of the leg. As the heel is elevated and starts the swing of the step, the calf muscles relax but the thigh muscles remain contracting. The venous valves close, preventing back flow of blood, and the venous pressure in the leg decreases, because the volume of blood remaining in the leg veins is not sufficient to fill these veins. When the foot retouches the floor, the calf muscles again contract and cause a slight rise in venous pressure. With the heel on the floor, at the end of the step, there is relaxation of the calf muscles as the weight of the body is redistributed to the two feet and a decrease in venous pressure

results. There is then a gradual rise in venous pressure as the veins fill with blood flowing in from the capillaries.

The decrease in pressure produced by walking can be explained by the fact that, immediately after the fall in pressure produced by the first step, the subject contracts his calf muscles in taking the next step before venous filling has been completed and thus additional blood is pumped out of the leg, causing a further drop in pressure when the calf muscles relax. This is repeated until a point is reached in walking whereas much blood comes into the vein from the capillaries as is pumped out of the leg with each step; this is the period of stable pressure. The veins fill from the arterial tree as the subject stands quietly at the end of the walk and the pressure gradually rises to the control standing level. If the venous valves are competent it is probable that the rate of this increase in pressure is dependent on the rate of arterial inflow to the leg and the volume of the leg veins (9).

Because of the effect of acceleration, produced by swinging the leg, on the strain gauge manometer and its associated hydrostatic system, there are artefacts in the recordings of venous pressure during walking. The pressure recordings obtained from the artificial hydrostatic column provided an approximate control as to the magnitude of these artefacts (figs. 3, 4, 6, 8, 9 and 10). The magnitude of the artefacts was reduced by overdamping the manometer system so that 0.2 second was required to register 95 per cent of the full response to an instantaneous pressure change. It is possible therefore that the rapid changes in venous pressure may not have been accurately recorded. Planimetric measurement of mean venous pressures, which has been utilized in this study, minimizes the errors due to instrumental artefacts.

Although no significant differences were found in the average venous pressures obtained during walking at various rates of speed in excess of 1.7 miles per hour, it is probable that significant differences would have been found if slower rates of walk had been used. The uniform increase in venous pressure which occurred during the slowing of the treadmill to less than 1.7 miles per hour at the end of the walk supports this contention. Beecher and his co-workers (14) found a lower venous pressure for moderate exercise than for light exercise. Their exercise consisted of walking 'in place' at a rate of 40 steps per minute, the severity of the exercise being regulated by adjusting the height to which the foot was lifted above the floor during each step. The average number of steps per minute associated with walking 1.7 miles per hour in the present study was 43 (39-45).

#### SUMMARY

Venous pressure in the great saphenous vein at the ankle was studied in 11 normal subjects in the recumbent, seated and quiet standing positions as well as during contraction of the leg muscles produced by standing on the toes and

while walking on a treadmill. Heart rate, heel position and pressure of a column of water extending from the third thoracic interspace to the tip of the catheter at the ankle were recorded simultaneously.

The venous pressure at the ankle averaged 11.7 mm. Hg (7.0-16) in the recumbent position, 56.0 mm. Hg (45.0-67.5) in the sitting position and 86.8 mm. Hg (78.5-92.6) in the resting standing position.

Venous pressure at the ankle in the resting sitting or standing positions was sufficient to support a column of blood to approximately the level of the third thoracic interspace at the sternum.

The changes in venous pressure produced by a single step were studied in 10 subjects. There was an average rise in pressure of 10 mm. Hg from the standing control level before the heel was lifted from the floor at the beginning of the step. An average fall of 52 mm. Hg (28.0-80.5) occurred with the foot off the floor. As the heel touched the floor there was a slight rise in pressure, followed by another fall to the previous low level while the heel settled on the floor and the body weight was redistributed. The pressure returned to the control level in an average time of 22.9 seconds (11.0-37.0) as the subject resumed the quiet standing position.

Subjects exercised on a level treadmill at 1.7, 2.6 and 3.3 miles per hour. Each step in the walk produced changes in venous pressure resembling the effect produced by a single step. The mean venous pressure decreased in every instance during the first 3 to 12 steps to an average stable value of 22.3 (11.0-30.6), 24.3 (8.5-38.0), and 23.6 (10.0-43.2) mm. Hg, respectively, which was maintained for the duration of the walk. After cessation of the walk the venous pressure returned to the previous standing control level in about one-half minute after cessation of the walk. No significant difference was demonstrated in the average mean pressures at the ankle during walking at the different speeds. The average decrease in pressure was approximately 60 mm. Hg, so that the mean venous pressure during walking was sufficient to support a column of blood approximately up to the level of the knee. Inclining the treadmill to 20° did not significantly alter the average decrease in pressure produced by walking.

The recorded mean pressure of a column of water extending from the outside of the ankle up to the third interspace was not changed during walking.

Contraction of the calf muscles by standing on the toes, without walking, caused a fall in venous pressure at the ankle. This decrease in pressure occurred without shortening of the hydrostatic distance from the catheter tip to the level of the right side of the heart and without the occurrence of significant accelerative forces on the manometer system.

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## *Use of Vasodilator Drugs and Body Warming in Evaluating Peripheral Vascular Disease<sup>1,2</sup>*

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IN THE STUDY of peripheral vascular disease in patients, it is desirable to determine the extent to which impairment of blood flow is due to the organic obstructive disease in comparison with that which is due to excessive vasospasm. In order to evaluate the latter, the vasospasm must be abolished by some means. Several new drugs having vasodilator properties have recently appeared. This paper is a comparison of the vasodilator effects of two of these drugs with that of body warming and a discussion of their use in evaluating the degree of vasospasm in patients with peripheral vascular disease.

### METHODS

Peripheral circulation was evaluated by recording the skin temperature of subjects placed in a constant temperature room under control conditions. Skin temperatures were recorded with an 8-point Leeds and Northrup micro-max, using iron-constantin thermocouples attached to the skin with a drop of collodion. The couples were constructed of no. 36-gauge wires placed between two facing strips of adhesive (1). The overall accuracy of the apparatus was approximately  $\pm 0.3^{\circ}\text{C}$ . Temperatures were recorded usually over the large and small toes of the foot, dorsum of the foot, on the shin, the thigh, the fingertip (usually the middle or little finger) and the forehead, together with the room temperature. That portion of the skin, the temperature of which was to be measured, was exposed to the room air. The remainder of the body was usually covered with a blanket unless exposure was necessary in order to induce vasoconstriction in the hands and feet. Blood flow and vasoconstriction were estimated from the relationship of the temperature of the skin to that of the room and forehead temperatures. For satisfactory interpretation, at least a  $10^{\circ}\text{C}$ . differential between room and forehead temperature is desirable. Minimal blood flow due to maximal vasoconstriction was considered to be present when the skin temperature approximated room temperature and

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maximal blood flow due to maximal vasodilation when the skin temperature approximated the forehead temperature. Association of vasoconstriction directly with blood flow was possible since arterial blood pressure remained essentially constant (1, 2).

The principal subjects were 10 volunteer normal medical students. The studies were carried out in a room at a temperature usually in the range of 17 to 21°C. This temperature induced strong vasoconstriction in all subjects as indicated by a progressive decline of the temperatures of the fingers, hands, toes and feet, so that they approached room temperature during the first hour after the subjects were placed in the room.

Vasodilator procedures studies were: *a*) warming of the torso by means of electric pads and reflector spot, 150-watt heat lamps directed to the torso and placed in such manner as not to effect the temperature of the skin which was in contact with the thermocouples; *b*) intramuscular injection of benzyl imidazoline<sup>3</sup> in 50-mg. doses repeated one or two times; *c*) intramuscular injections of 500 to 800 mg. of tetraethyl ammonium<sup>4</sup>; *d*) a combination of one of these drugs with body warming.

No vasodilator procedure was used until maximal vasoconstriction had been induced. Following the onset of vasodilation the subject was kept in the cool environment until vasoconstriction had again returned when another vasodilator procedure was tested. Each subject was tested over a period of five to eight hours. Three to six vasodilator procedures were tested in each subject (av. 3.4).

## RESULTS

Vasodilation was most readily obtained in *subject WCB* (fig. 1) with each procedure tested. He was kept at a room temperature between 25 and 19°C., averaging around 21°C. Forehead temperature ranged between 35 and 30°C., toe temperature was at room temperature at the start of recording and finger temperature averaged 32°C. at the start of the recording but dropped rapidly, reaching a minimum of 22°C. A temporary rise in finger temperature to 30° followed the first injection of benzyl imidazoline but the finger temperature then declined to 24°C. After the application of heat to the body, the finger temperature rose rapidly, exceeding slightly the forehead temperature. At this time the toe temperature also began to rise and reached a maximum of 34°C. After discontinuing body warming, both finger and toe temperatures slowly dropped, the toe temperature to 23° and the finger temperature to room temperature. At this time tetraethyl ammonium was given intramuscularly

<sup>3</sup> 2-benzyl-4,5-imidazoline HCl (Priscol). The Priscol was supplied by Ciba Pharmaceutical Products, Summit, N. J.

<sup>4</sup> Tetraethyl ammonium chloride (Etamon). The Etamon was supplied by Parke, Davis & Company, Detroit, Mich.

and the toe temperature again rose rapidly to forehead temperature. The finger temperature remained a little above the room temperature. This is the best example of a response of the toe temperature to body warming and to tetraethyl ammonium which we obtained in this series.

*Subject C* (fig. 2) was one in which it was most difficult to induce vasodilation. He was kept at a room temperature between 21 and 17.5°C. His forehead temperature varied between 34.5 and 32°C. At the start of the test the toe temperature approximated room temperature and the finger temperature was about 1.5°C. higher. In this instance, tetraethyl ammonium, 500 mg., had no effect. Application of heat to the body caused the finger temperature to rise to a maximum of 30° following which it dropped rapidly when the

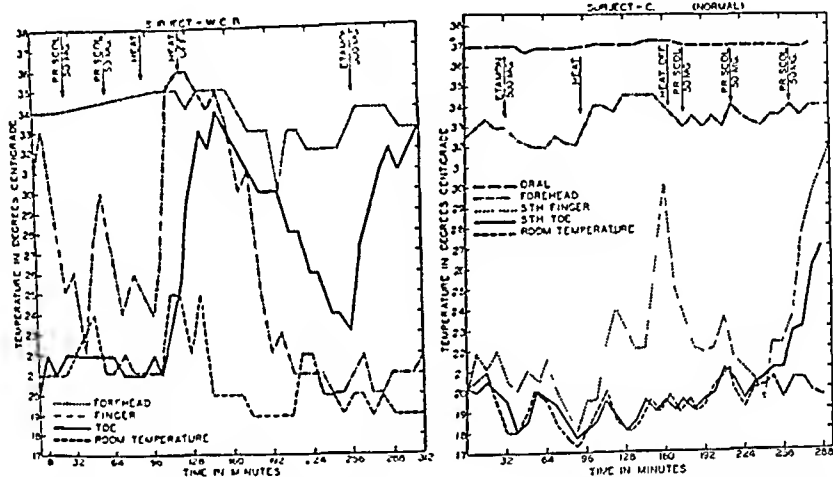


Fig. 1 (left). CUTANEOUS TEMPERATURE RESPONSES in a highly reactive normal subject.

Fig. 2 (right). CUTANEOUS TEMPERATURE RESPONSES in a normal subject who tended to maintain vasoconstriction.

heat was discontinued. Three injections of benzyl imidazoline were then given and following the third injection (total of 150 mg.) both finger and toe temperatures began to rise rapidly. They were still rising at the time the study was discontinued.

Table 1 shows the results in the 10 normal subjects. Body warming increased blood flow more consistently and to higher levels in the fingers than in the toes and was more effective than either tetraethyl ammonium or benzyl imidazoline in this regard. In general, tetraethyl ammonium did not have a consistent effect on the blood flow in the fingers. The blood flow in the toes was elevated somewhat more consistently and to higher levels by tetraethyl ammonium than by body warming. Benzyl imidazoline increased blood flow in both fingers and toes more consistently and to a greater degree than tetraethyl ammonium. It was more effective than body warming in increasing



blood flow in the toes but less effective in the fingers. The most effective procedure for relaxing vasospasm in both hands and feet appeared to be a combination of body warming plus intramuscular injection of benzyl imidazoline. This produced the greatest average increase in blood flow and the highest individual increase in both fingers and toes.

In the 10 normal subjects tested in table 1, body warming consistently produced a good response in the fingers, but caused warming of the toes in only one subject. Tetraethyl ammonium failed to produce a response in fingers or toes in 5 subjects. The toes responded well in the remainder but the fingers showed good vasodilation in only one and partial vasodilation in one subject. There were four instances in which benzyl imidazoline alone in a dose of 50 to 100 mg. failed to produce any effect, four instances in which good responses

TABLE 1. SUMMARY OF RESULTS IN 10 NORMAL SUBJECTS

TEST	FINGERS			TOES		
	Number of observations	Change from control temperature, °C.		Number of observations	Change from control temperature, °C.	
		Range	Average		Range	Average
Body warming.....	7	+9.5 to +14.2	+11.5	7	-1 to +4	+0.5
Etamon, 500 mg., I. M....	10	-1 to +7	+0.5	9	0 to +10	+3.7
Priscol, 50-150 mg., I. M...	9	0 to +10.5	+3.7	9	-1 to +12.5	+3.8
Priscol, 50-150 mg. + body warming.....	8	+5 to +16.5	+10.9	8	0 to +13	+9.2

Note: In each instance the control temperature was at or within 1° to 2° of room temperature.

occurred in fingers and toes and one in which the toes failed to respond but a good response was obtained in the fingers. When a combination of benzyl imidazoline plus body warming was used there was no instance of failure to produce a good increase in blood flow in the fingers and only one instance of failure in the toes. The fingers and toes usually responded equally well.

#### DISCUSSION

The better response of the hands than the feet to body warming confirms previous observations that the regulation of blood flow in the hand by the vasoconstrictor center is more labile than that of the foot. The vasoconstrictor pathways to the hand appear to be less accessible to block by tetraethyl ammonium than those to the foot. In fact, not infrequently vasoconstriction in the hand accompanied vasodilation in the foot when the latter was induced by tetraethyl ammonium; the significance of these findings in terms of the known ganglionic blocking actions (3-7) and the lack of local vascular effects

(g) of this drug is not clear. In view of the postural hypotension associated with tetraethyl ammonium, it may be that this drug has greater access to the vasoconstrictor fibers associated with postural than to those associated with temperature regulation. The approximately equal effect of benzyl imidazoline on the blood vessels of the hands and feet might be anticipated from the fact that part or perhaps all of its effect is due to peripherally induced vasodilation (8, 9).

In evaluating peripheral vascular disease it is desirable to use a procedure which may be expected consistently to produce vasodilation in normal subjects. It is also desirable to record vasodilation in a normal extremity in the patient in order that one may be assured that the vasodilator procedure is effective in the particular patient. This is illustrated in the following paragraphs.

A. Concomitant elevation of the finger and toe temperatures occurred most consistently when benzyl imidazoline plus body warming was used. The occurrence of vasodilation in one extremity may therefore be used as an index that the dose was presumably large enough that vasodilation should have occurred in all extremities. Failure of adequate vasodilation to occur in one extremity under these conditions would suggest that organic occlusive disease may be present in the extremity which failed to demonstrate a rise of skin temperature.

B. Tetraethyl ammonium usually produced vasodilation in the toes with no change in finger temperature. Therefore a failure of the finger temperature to increase with this drug should not necessarily be interpreted as meaning that adequate dosage has not been used. On the other hand, failure of toe temperature to rise when finger temperature rose after tetraethyl ammonium would be highly suggestive of occlusive vascular disease in the foot.

C. Elevation of finger temperature without change of toe temperature was frequently seen after body warming. Therefore, a failure of toe temperature to increase with finger temperature after body warming could not necessarily be interpreted as indicating occlusive vascular disease in the foot but a failure of finger temperature to increase concomitantly with toe temperature in response to body warming would be highly suggestive of occlusive vascular disease in the hand.

An example of the use of these procedures in the study of a patient is presented in figure 3. *Mrs. P.* began complaining of pains in the right leg and calf one and one half years prior to this study. One year later she noted intermittent claudication and beginning dependent rubor in the left leg. At the time of this temperature study she was found to have diabetes, her blood cholesterol was 230 mg/100 cc. and her blood pressure 160/80. The dorsalis pedis, posterior tibial and popliteal artery pulsations were palpable on the right but were not felt on the left. Marked dependent rubor was noted in the left foot. *Mrs. P.* was studied at an average room temperature of 19°C. Her

forehead temperature averaged  $31^{\circ}$ . During the first two hours, the temperature of the right and left large toes progressively dropped, reaching ultimately a temperature about  $2^{\circ}\text{C}$ . above room temperature. The finger temperature remained at forehead temperature until just before an injection of tetraethyl ammonium, when the finger temperature dropped to  $23^{\circ}$ . The injection of 500 mg. of this drug failed to produce vasodilation in either fingers or toes. Heat applied to the abdomen caused vasodilation in the fingers, the temperature rising to within 1 to  $2^{\circ}$  of forehead temperature but no change occurred in the toes. Following one injection of 50 mg. of benzyl imidazoline, the right

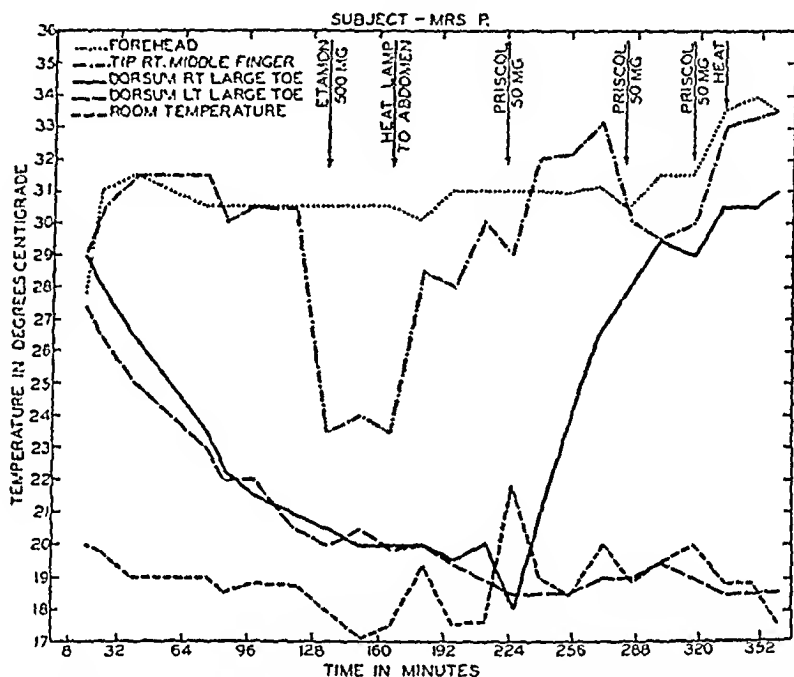


Fig. 3 RESPONSE TO THE SAME DRUGS in a patient with occlusive vascular disease of the left foot.

large toe temperature rose rapidly to  $29^{\circ}$ . Despite two additional injections of the drug plus body warming, which caused some increased vasodilation in the finger and right toe, the temperature of the left large toe remained at room temperature. This patient is believed to have occlusive vascular disease of the left foot.

The side reactions with tetraethyl ammonium included blurring of vision, dryness of the mouth, metallic taste on a few occasions and warmth and flushing. No difficulty was experienced in any of the subjects due to a decline in arterial blood pressure inasmuch as all subjects were kept horizontal for at least an hour after the last injection of this drug.

Benzyl imidazoline in doses of 50 to 200 mg. has been given to 30 subjects. It consistently caused 'goose pimples' of the skin, chilliness, a sensation as if the hair were standing on end, particularly in the back of the neck, and occa-

sionally caused nausea. Some of the symptoms could be relieved by eating. In a number of individuals, marked congestion of the conjunctiva was noted. No consistent change in arterial blood pressure was noted, and no other untoward symptoms were observed.

It is our impression after using these methods in comparison that benzyl imidazoline or tetraethyl ammonium plus body warming is less uncomfortable for the patient and may be equally as satisfactory for the production of vasodilation as spinal anesthesia or sympathetic block.

#### SUMMARY

Blood flow and vasoconstriction in the skin of the extremities was estimated by recording the temperature of the skin of the extremities, the room temperature and the forehead temperature with iron-constantin thermocouples. Vasoconstriction was induced by placing the subject in a cool environment ( $17-21^{\circ}\text{C}.$ ). After the development of vasoconstriction the vasodilator effects of tetraethyl ammonium and benzyl imidazoline injection intramuscularly and warming the body with heat lamps were recorded. All three induced vasodilation in some normal subjects. Body warming was most effective in abolishing vasoconstriction in the hand and tetraethyl ammonium, in the foot. Benzyl imidazoline was about equally effective on both hand and foot. Tetraethyl ammonium or benzyl imidazoline plus body warming most consistently induced vasodilation in both hand and foot.

From these results it was concluded that one could be most certain that vasospasm had been abolished by the use of 150 mg. or more of benzyl imidazoline plus body warming. An example of the use of benzyl imidazoline plus body warming in a patient with occlusive vascular disease of one foot was presented.

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## *Some Effects of Albumin Infusions on Renal Function and Electrolyte Excretion in Normal Man*

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CONCENTRATED HUMAN ALBUMIN has recently been used in the treatment of the nephrotic syndrome (1-7, 11), cirrhosis (7-11) and other hypoalbuminemic conditions with edema (1, 7, 11). While the exact limits of its therapeutic potentialities have yet to be defined, it is clear that albumin can produce large diureses of salt and water in certain of these conditions.

The precise mechanism of the diuretic action of albumin is obscure. In most cases, administration of this substance increases the serum albumin concentration and expands the plasma volume. No correlation has been observed between the extent of these changes and the excretory response (3). Diuresis is a function of neither the incidence nor the magnitude of proteinuria resulting from albumin (3, 8). It has been the clinical impression of several observers that the extent of the diuresis is roughly proportional to the amount of edema present (3, 8, 10). Data on the effect of albumin on the salt and water exchange of normal subjects have not yet been published.

Recently, some measurements have been made of the changes in renal function with albumin therapy. Luetscher (2, 12) found that albumin infusions raised the mannitol clearance of nephrotics and that the calculated tubular reabsorption of sodium per unit filtered was greatly reduced. Eder and his associates (4) reported that significant increases in the clearances of mannitol and endogenous creatinine occurred during the albumin-induced diureses of 3 nephrotic patients. Bradley and his coworkers (5) found similar rises in mannitol and para-aminohippurate clearances in nephrotics and normals, but no detailed data have been published. Recently, Cargill (13) reported that rapid infusion of albumin into normal subjects resulted in immediate small increases in inulin clearance and relatively larger increases in para-aminohippurate (PAH) clearance. Much larger changes in both these functions were induced in two nephrotic patients. In all subjects renal tubular extraction of PAH was significantly reduced after albumin infusion. No data have yet been presented which might clarify the relation of these functional changes to the concomitant changes in water and electrolyte excretion.

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This paper reports observations made on certain of the immediate renal and hemodynamic effects of the administration of 75 gm. of salt-poor human albumin to normal subjects, in an attempt to answer the following questions: 1) How do the reactions of normal subjects to the rapid injection of albumin differ from those already described in patients with hypoproteinemia and edema? 2) What are the immediate responses of the normal kidney to the sudden expansion of blood volume induced by albumin? 3) Can any changes in electrolyte excretion under these circumstances be correlated with changes in filtration rate as estimated by mannitol clearance, and what are the relative rôles of glomerular filtration and tubular reabsorption in producing these changes?

#### MATERIALS AND METHODS

*a. Experimental Procedure.* Data are presented from 12 experiments on 3 normal young adult males. In 26 preliminary experiments, not reported here, the conditions for obtaining 3 consecutive clearance periods of about one hour each, characterized by good urine flows and reproducibly constant rates of sodium and chloride excretion, were investigated. Various schedules of oral priming with water and hypotonic saline solutions, and of intravenous saline priming were tried, on the basis of which the final 12 experiments were planned according to table 1.

In 6 experiments, during the second clearance period, 75 gm. of salt-poor concentrated human albumin<sup>2</sup> (300 cc. of solution containing 155 mEq/l. of sodium, 20 mEq/l. of chloride and negligible amounts of potassium) were introduced intravenously in an average time of 46 minutes. In 3 of the 6 control experiments, 300 cc. of normal saline was substituted for the albumin infusion. In the other 3 controls (*experiments 1, 2 and 3 in table 2*) no infusion was given. The same quantity of mannitol was injected in all 12 experiments.

*b. Methods.* Sodium and potassium concentrations in serum and urine were measured with the flame photometer by the method of Hald (14), duplicate determinations being required to check within 2 per cent for sodium and 5 per cent for potassium. Chloride determinations in serum were made by the method of Hald (15), and in urine by a modification of the method of Volhard and Harvey (16).

Mannitol concentrations in serum and urine were measured by the method of Elkinton (17), the standard error for which is 88 mg. per cent in urine and 1.2 mg. per cent in serum. Hemoglobin concentrations in blood were measured in alkaline solutions in an Evelyn colorimeter. Hematocrit determinations were made with Daland tubes. Both procedures were done on blood defibrinated

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<sup>2</sup> Serum albumin used in this study was prepared by the American Red Cross from blood of volunteer donors. The conclusions are those of the authors and do not necessarily reflect the policy of the National Blood Program of the American Red Cross.

anaerobically by the method of Eisenman (18). Venous pressure measurements were made directly from an antecubital vein with a lumbar puncture manometer, the sternal angle being taken as the zero reference point.

*c. Calculations.* Electrolyte excretion rates and glomerular filtration rates were corrected to standard surface area. The factors used were 0.90 for ASR, 0.86 for ERP and 0.95 for AVG. Glomerular filtration rate (GFR) was

TABLE 1. PROTOCOL OF MODEL EXPERIMENT<sup>1</sup>

TIME	INTAKE <sup>1</sup>	ACTIVITY	URINE SAMPLE <sup>2</sup>	BLOOD SAMPLE <sup>4</sup>	PROCEDURE
hr.					
-6.5	250 cc/os each hour	Usual daily			
-2.0		Semi-reclining on couch	Voids (discarded)		
-0.5			Urine blank	Serum blank	Mannitol injection <sup>6</sup>
0			Voids (discarded)	1	
+1.0			1	2	Control clearance period
+2.0			2	3	Experimental clearance period
+3.0			3	4	Recovery clearance period

<sup>1</sup> Subjects began to drink after their noon meal and were fasting throughout the rest of the experiment which lasted until 10-11 p.m. <sup>2</sup> 0.2% saline was used in some experiments for reasons given in the text. See table 2 for method of priming in each experiment. <sup>3</sup> Subjects voided in erect position without the use of a catheter. <sup>4</sup> Injections of mannitol and experimental solutions were made via separate venapunctures. <sup>5</sup> 25 gm. in 100 cc. H<sub>2</sub>O were given intravenously in about 5 minutes.

assumed to be identical with the clearance of mannitol, calculated for the single injection method from the equation:

$$\text{GFR} = UV \times S \times \frac{2.3 \times \log \frac{P_1}{P_2}}{P_1 - P_2}$$

where UV is the urinary excretion rate of mannitol, S is the surface factor mentioned above, and the last term in the equation is the mean plasma concentration between two points, P<sub>1</sub> and P<sub>2</sub>, which lie on the exponential curve of declining plasma concentration of mannitol.

Electrolyte filtration rates were calculated from the product of the values for GFR and serum electrolyte concentration, corrected for the water content of serum (calculated from the serum protein value in some instances, and assumed



TABLE 2. EXPERIMENTAL DATA

EXPER.	SUBJECT	PRIMING METHOD •	TIME OF PERIOD	EXCRETION RATES				GFR
				H <sub>2</sub> O cc.	Na mEq.	Cl mEq.	K mEq.	cc/min/ 1.73 m <sup>2</sup>
				min/1.73m <sup>2</sup>				
Controls								
1	AVG	H <sub>2</sub> O	63	3.17	.250	.205	.060	80
			60	4.42	.226	.235	.080	82
2	ASR	"	57	4.17	.259	.222	.062	71
			57	4.27	.201	.163	.079	102
			58	7.15	.165	.119	.067	88
3	ERP	"	59	4.22	.141	.101	.031	94
			58	7.24	.282	.238	.039	107
			58	6.33	.270	.214	.043	90
4	AVG	0.2% Sal.	60	3.97	.216	.170	.033	84
			60	2.20	.192	.146	.038	84
			58	4.30	.179	.129	.038	73
5	ASR	"	54	6.10	.188	.128	.037	73
			51	2.43	.226	.225	.040	100
			53	4.70	.179	.179	.042	89
6	ERP	"	48	4.12	.178	.172	.043	79
			62	4.42	.291	.247	.066	84
			59	6.50	.306	.245	.055	71
7	ASR <sup>1</sup>	"	59	4.43	.305	.230	.046	64
			61	3.62	.329	.346	.040	106
			61	2.68	.228	.216	.033	81
			53	2.58	.101	.122	.032	72
Albumin experiments								
8	AVG	H <sub>2</sub> O	60	5.34	.334	.268	.099	76
			71	5.88	.285	.141	.142	79
			77	6.05	.185	.124	.104	69
9	ASR	"	75	7.25	.300	.247	.029	89
			74	3.70	.187	.106	.033	76
			76	4.74	.068	.058	.039	82
10	ERP <sup>2</sup>	"	63	6.38	.171	.142	.040	
			67	3.96	.181	.089	.047	
			65	5.86	.137	.054	.047	
11	AVG	0.2% Sal.	57	4.32	.300	.269	.044	103
			69	4.30	.256	.158	.078	108
			52	6.57	.196	.134	.057	94
12	ASR	"	62	3.46	.228	.252	.049	103
			64	2.95	.220	.118	.035	94
			52	4.95	.134	.090	.100	87
13	ERP	"	55	3.27	.278	.260	.054	77
			74	3.13	.298	.186	.085	79
			54	3.81	.123	.091	.080	66

<sup>1</sup> Data from unsatisfactory control experiment included here for reasons stated in text. <sup>2</sup> Glomerular filtration rates from *exper. 10* omitted because of unsatisfactory laboratory determinations.

to be 93 per cent in the others), and the Donnan factor for each ion (0.92 for sodium, 1.05 for chloride and 0.80 for potassium).

Excretion ratios of electrolytes and water were calculated by dividing

excretion rates of these substances by their corresponding filtration rates. Changes in plasma volume (PV) were estimated from the changes in hemoglobin (Hgb) and hematocrit (Hkt) according to the formula:

$$\frac{PV_2}{PV_1} = \frac{Hgb_1}{Hgb_2} \times \frac{(1 - Hkt_2)}{(1 - Hkt_1)}$$

where the numbers in subscript indicate the values at the beginning and the end of a given period respectively. The equation can be derived from the single assumption that the total amount of circulating hemoglobin remains constant.

## RESULTS

The experimental data are presented in tables 2 and 2a.

*a. Control Experiments.* Urine flows increased during the experimental hour in all experiments but one, and decreased during the recovery hour in all experiments but one. However, the total changes from the first to the third clearance periods were quite variable, showing both increases and decreases. Sodium and chloride excretion rates were essentially constant or declined slightly from the first to the third clearance periods. The small rises in the excretion rates of sodium in *experiment 6* and of sodium and chloride in *experiment 1*, despite concomitant falls in glomerular filtration rates are considered to be barely outside the experimental error of the techniques used. Potassium excretion rates were somewhat more variable than those of sodium or chloride and were not related to the latter. Glomerular filtration rates declined in all experiments though the degree of fall was in some instances within the error of the determination.

Changes in electrolyte excretion and glomerular filtration, from the first to the third clearance periods, are summarized in table 3.

Serum electrolyte concentrations were all within normal limits. They remained essentially constant except in *experiment 6*, where the sodium concentration rose 5 mEq/l.

A thirteenth experiment (*no. 7*) conducted as a control on ASR was considered unsatisfactory because of the discomfort caused by attempts to obtain samples of blood. The experiment was repeated to provide the second satisfactory control on ASR (*experiment 5*). The results of the unsatisfactory experiment have been included in table 2 because of their similarity to those obtained after injection of albumin, but they were omitted from statistical analyses. Pain and anxiety are known to reduce the glomerular filtration rate and effective renal blood flow (19, 20), and to cause oliguria (21), but their influence on electrolyte excretion has hardly been studied.

*b. Albumin Experiments.* Urine flows remained almost constant or declined during the experimental hour and rose in every instance during the recovery hour. These changes were opposite to, and significantly different from,

TABLE 2A. EXPERIMENTAL DATA

EXPER.	FILTRATION RATES				Hgb gm.	Hkt. %	PLASMA VOLUME CHANGE %	VENOUS PRES- SURE mm. Sal.	EXCRETION RATIOS <sup>1</sup>			
	H <sub>2</sub> O cc.	Na mEq.	Cl mEq.	K mEq.					H <sub>2</sub> O	Na	Cl	K
	min/1.73m <sup>2</sup>				%	%	%					
I	74	10.9	8.6	.272					.043	.023	.024	.220
	76	11.4	8.9	.270					.058	.020	.027	.297
	65	9.8	8.2	.257					.064	.026	.027	.238
2	94	14.3	11.2	.338					.043	.014	.015	.233
	81	12.3	9.9	.289					.086	.014	.012	.232
	87	13.1	10.5	.309					.054	.011	.010	.103
3	100	14.8	11.8	.367					.077	.019	.020	.106
	84	12.4	10.0	.314					.078	.022	.021	.136
	78	11.6	9.4	.282					.046	.019	.018	.117
4	78	11.5	9.4	.275					.028	.017	.016	.138
	61	10.1	8.3	.246					.070	.018	.016	.155
	61	10.1	8.3	.246					.100	.019	.015	.149
5	93	13.2	11.3	.319					.026	.017	.020	.125
	82	11.7	10.0	.298					.057	.015	.018	.142
	73	10.3	8.9	.264					.057	.017	.019	.162
6	78	11.0	9.3	.302					.055	.029	.026	.219
	66	9.5	7.9	.262					.098	.032	.031	.208
	60	8.7	7.2	.234					.074	.035	.032	.198
7	99	14.7	11.4	.403					.037	.022	.030	.099
	75	11.3	8.8	.321					.026	.020	.025	.102
	67	10.0	7.8	.276					.039	.010	.016	.116
8	70	10.5	8.8	.290	13.2	39.7		110	.076	.032	.031	.340
	74	10.7	8.7	.262	11.9	35.0	+19	210 <sup>2</sup>	.080	.027	.016	.542
	64	9.2	7.5	.206	11.9	36.1	+17	65	.094	.020	.017	.505
9	83	12.1	9.6	.308	13.5	43.5		70	.087	.025	.026	.094
	70	10.3	8.2	.241	12.2	39.3	+19	55	.053	.018	.013	.138
	76	11.2	8.8	.260	12.7	38.5	+16		.062	.006	.007	.148
10					13.9	40.5		120				
					11.9	37.9	+22	60				
					12.1	37.2	+21	115				
11	96	14.1	11.9	.364	12.3	37.5		110	.045	.021	.023	.121
	100	14.7	12.5	.387	11.1	34.1	+20	145	.043	.017	.013	.200
	87	12.8	10.9	.318				80	.076	.015	.012	.179
12	96	13.9	11.3	.355	12.9	40.8		110	.036	.016	.022	.139
	88	12.8	10.2	.320	11.6	36.5	+19	75	.034	.017	.012	.109
	81	12.0	9.3	.285					.061	.011	.010	.284
13	71	11.0	9.0	.258	13.5	46.6		90	.046	.025	.029	.208
	74	12.9	8.7	.290	12.2	42.0	+20	70	.043	.023	.021	.291
	61	9.4	7.2	.228	12.7	41.0	+17	140	.062	.013	.013	.351

<sup>1</sup> Excretion ratio =  $\frac{\text{Quantity excreted/min/1.73m}^2}{\text{Quantity filtered/min/1.73m}^2}$ .

in the opposite arm. <sup>2</sup> This venous pressure was checked

those noted above in the control experiments (P less than .02 for the experimental hour and less than .05 for the recovery hour). The total changes from the first to the third clearance periods were quite variable, as in the control experiments.

Sodium and chloride excretion rates decreased in every experiment, the falls from the first to the third clearance periods being greater than in the controls. Furthermore, it was noted that the declines in sodium excretion took place mainly in the recovery hour, whereas the falls in chloride excretion rates occurred during both experimental and recovery hours. Potassium

TABLE 3. PERCENTAGE CHANGES IN ELECTROLYTE EXCRETION RATES AND RATIOS<sup>1</sup>, AND GLOMERULAR FILTRATION RATES, FROM THE FIRST TO THE THIRD CLEARANCE PERIODS

(RECOVERY HOUR-CONTROL HOUR)  
CONTROL HOUR

EXPER.	RATES			GFR	EXCRETION RATIOS		
	Na	Cl	K		Na	Cl	K
<i>Controls</i>							
1.....	+4	+8	+3	-11	+13	+12	+8
2.....	-30	-38	-61	-8	-2	-33	-56
3.....	-23	-29	-15	-22	0	-10	+10
4.....	-2	-12	-3	-13	+12	-6	+8
5.....	-21	-24	+8	-21	0	-5	+30
6.....	+5	-7	-30	-24	+21	+23	-10
Means.....	-11	-17	-16	-16.5	+7	-3	-2
S.D.'s.....	±15	±17	±26	±6.6	±8	±19	±30
<i>Albumin experi- ments</i>							
8.....	-45	-54	+5	-9	-38	-45	+49
9.....	-77	-77	+34	-8	-76	-73	+57
10.....	-20	-62	+18				
11.....	-35	-50	+30	-9	-29	-48	+48
12.....	-41	-64	+104	-16	-31	-55	+104
13.....	-56	-65	+48	-14	-48	-55	+69
Means.....	-46	-62	+40	-11	-44	-55	+65
S.D.'s.....	±19	±9	±32	±4	±20	±11	±23
<i>T-test</i>							
t.....	3.5	5.8	3.3	2.0	6.0	5.3	4.1
P.....	.01-.02	<.01	.02-.05	.05-.10	<.01	<.01	<.01
<i>Variant analysis</i>							
F.....	7.9	66.3	6.8				
P.....	.01-.05	<.01	.01-.05				

<sup>1</sup> Excretion ratio =  $\frac{\text{Quantity excreted/min/1.73 sq. m.}}{\text{Quantity filtered/min/1.73 sq. m.}}$

excretion rates increased from the first to the third period in every instance, rises during the hour of albumin infusion occurring in every experiment but one.

Statistical treatment of these data by the methods of variant analysis<sup>3</sup> yielded values for F and P shown in table 3, which indicated that the differences

<sup>3</sup> We are indebted to Dr. Chester I. Bliss of the Department of Pharmacology, and to Dr. John H. Watkins of the Department of Public Health, Yale University School of Medicine, for setting up these analyses for us.

between control and albumin experiments were highly significant for chloride, and significant for sodium and potassium.

Glomerular filtration rate declines tended to be less than those of the control experiments, but were not significantly different from them (*t* equals 2.0). Serum electrolyte concentrations remained constant and were not different from those obtaining during the control experiments. The plasma volume increased by an average of 20 per cent (range 19–22%) during the albumin infusions, remaining expanded throughout the recovery hour at the same level. If it is assumed that each subject had an initial plasma volume of 45 cc/kg., the quantity of fluid entering the circulation during the infusions averaged 9 cc/gm. of albumin.

Venous pressure changed variably during the infusions, falling 15 to 60 mm. saline in subjects *ASR* and *ERP*, and rising 35 to 100 mm. saline in subject *AVG*. Blood pressure determinations made in some of the experiments showed no significantly greater changes than were observed in the controls. Reactions were not noted except in *experiment 13*, where a mild pyrogenic response consisting of malaise, chilly sensations and a rise in oral temperature to 100.8, began about one-half hour after the albumin infusion and lasted about two hours. In a few other experiments, transient headaches were noted. Urine albumin tests (acidification and heating), done on all samples obtained in 3 of the 6 albumin experiments, were negative.

#### DISCUSSION

Interpretation of the data presented above must be made with caution because of the conditions under which they were obtained. In order to avoid significant errors in bladder emptying, large urine flows were promoted by the ingestion of 250 cc. of fluid per hour. In half the experiments, 0.2 per cent saline was used for priming to prevent the mild dehydration and salt depletion which may attend the continuous administration of water (22–24). There were, however, no significant differences between the saline-primed and water-primed groups in their responses to albumin.

The potent chloruretic effect of mannitol (25) must be considered, not only for its tendency to produce salt depletion, but also because of its modification of the absolute rates of electrolyte excretion during the experimental clearance periods. Recent reports (26, 27) indicate that mannitol clearance may be only a close approximation of the glomerular filtration rate. There is no evidence, however, that changes in mannitol clearance are not proportional to changes in actual glomerular filtration.

Exercise or the passive erect position causes progressive decreases in the glomerular filtration rate and effective renal blood flow (19, 28–30). Quiet standing will also reduce the rate of chloride excretion (31). Our observations were made with the subjects reclining with their trunks elevated approximately

60° from the horizontal, which is, in effect, a variety of passive erect posture. Three consecutive hourly mannitol clearances obtained on two of our subjects in a completely reclining position were essentially constant. It would seem likely, therefore, that the tendency for both mannitol clearances and sodium and chloride excretion rates to decline slightly in the control experiments are due at least in part to the effects of prolonged orthostasis. The slight changes in the salt excretion rates of our controls may also reflect the normal diurnal fluctuation (32-34). Whatever the influences involved, they are probably adequately controlled, since all experiments were performed under similar conditions of hydration at the same time of day, using mannitol in identical amounts, and with subjects in similar positions for the same length of time.

The absence of diuresis and the decline in sodium and chloride excretion after the administration of albumin in these experiments contrast sharply with the marked salt and water diuresis previously reported in nephrotics. An explanation of these differences might be sought in the concomitant changes produced in renal dynamics. Whereas albumin infusions in nephrotics cause large increases in glomerular filtration rates, (13), they had a negligible effect on mannitol clearances in these experiments<sup>4</sup>. The decline in salt excretion, however, is not easily explained.

If one arbitrarily chooses to express tubular activity as the proportion of filtered electrolyte that is excreted, i.e., as the fraction  $E/F^5$  (mEq. electrolyte excreted/min/1.73 sq. m. divided by the mEq. electrolyte filtered/min/1.73 sq. m.), the relation of this fraction to the excretion rate can be analyzed. In table 3 are listed the percentage changes in excretion rates and  $E/F$  from the control to the third hour for each of the 3 ions studied. Absolute differences were not used because the absolute level of electrolyte excretion in the control hour depends, in large measure, on the daily salt intake of the subjects. Comparison of the percentage changes in salt excretion rates with those of the excretion ratios ( $E/F$ ) during the albumin experiments listed in table 3 indicates a clear concordant association of these two terms. This relationship may be seen during some of the spontaneous changes in salt excretion occurring in the control experiments. It will be noted in table 3, however, that in two control experiments (nos. 4 and 6) there were increases in sodium or chloride ratios in the face of decreases in electrolyte excretion.

Table 3 also lists the percentage changes in glomerular filtration rate from the first to the third hours. In experiments 1, 4, and 6 there were increases

<sup>4</sup> Cargill's data show very slight increases of inulin clearance in normals following albumin infusions. He used a more rapid rate of infusion than was employed in the experiments reported here.

<sup>5</sup> An important reason why excreted/filtered is chosen as an index of tubular transfer rather than reabsorbed/filtered or the absolute quantity of electrolyte reabsorbed per minute is that the first term has the greatest relative variation in value.

in salt ratios despite probably significant decreases in glomerular filtration rate, indicating some dissociation between glomerular and tubular function with respect to salt excretion.

It should be recognized that these data do not conclusively assign to the tubules the responsibility for changes in electrolyte excretion produced by albumin infusion, because the error in measurement of filtration rate is so large in relation to the absolute value of the excretion rate.

Cargill (13) has shown that albumin infusions increase para-aminohippurate clearance, but decrease its extraction ratio, both in nephrotics and normals. He suggests that these changes may be attributable to diversion of part of the increased renal blood flow through arterio-venous shunts in the kidney. Presumably the renal blood flow increased in our experiments also. It is difficult to see how this could be responsible for the decreased excretion of salt.

The plasma volume expansion in these experiments, calculated from an assumed normal volume and the observed changes in hemoglobin and hematocrit averaged 9 cc/gm. of albumin injected. On teleological grounds one might have anticipated that any immediate renal reaction to an expanding blood volume would be in a compensatory direction. It might be argued, however, that diuresis could be delayed. Experiments of a longer duration are needed to explore this possibility.

We have performed one such experiment in which 75 gm. of albumin per day were administered for 4 consecutive days to a normal subject in bed on a constant (3.17 gm.) sodium intake. During these 4 days, sodium excretion was reduced from the control level of about 3.0 gm/day to 1.8-2.2 gm/day. There was no increase in urine volumes. When albumin was stopped, sodium excretion returned to control levels. Bodyweight was approximately constant during the entire period of study, and the serum sodium concentration did not rise significantly. Falls in hemoglobin and hematocrit indicated a large sustained expansion of the blood volume. In this experiment, at least, there was no evidence of a delayed diuresis.

The rapid increase of the colloid osmotic pressure of the blood, by stimulating the posterior pituitary secretion (21), may be responsible for the relative retention of water during the albumin infusions. Retention of salt, however, was clearly independent of water, since salt excretion declined in the recovery hour while urine flows rose.

In contrast to sodium and chloride, potassium excretion appeared to be accelerated by the albumin infusions. Serum potassium concentrations, however, remained constant. The independent behavior of potassium exemplified here is quite in keeping with data from a number of sources which indicate that this ion is reabsorbed less completely than sodium and chloride (35, 36) and probably is excreted by a different mechanism (37, 38). It is possible that

albumin caused a discharge from cells of potassium which was immediately excreted.

### SUMMARY

In 6 controlled experiments 75 gm. of human salt-poor albumin were injected rapidly into 3 normal subjects during a large water and mannitol diuresis. This resulted in an immediate 20 per cent increase in plasma volume, a relative reduction of urine flow, no significant change in mannitol clearance, a decrease in sodium and chloride excretion and an increase in potassium excretion. The changes in sodium and chloride excretion may be related to alterations in tubular activity as indicated by changes in the fraction 'excreted/filtered', the numerical values of which are derived under the assumption that mannitol clearance and glomerular filtration rate are equivalent.

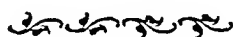
We are grateful for the advice of Dr. John P. Peters and Dr. J. Russell Elkinton. Miss Pauline Hald gave us invaluable instruction in analytical techniques.

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## *Relation of Age to Physiological Responses of the Older Boy (10-17 Years) to Exercise<sup>1</sup>*

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ROBINSON'S STUDY (1) of groups of children and adults of various ages has shown that the physiological response to exercise may vary both with the age of the child and that of the adult. The present report extends the work of Robinson by studying more thoroughly the ages between 10 and 17 years. These ages include the period of adolescence during which physiological and anatomical changes associated with rapid growth and maturation might be expected to influence the functional response to exercise. The study was undertaken with two aims in mind, to add to the knowledge of the adolescent by comparing his responses to exercise with those of younger children, and to establish criteria based upon knowledge of the normal by which abnormalities of functional response in disease can be judged.

### METHODS AND PROCEDURE

The methods used were essentially those developed by Dill and his collaborators at the Harvard Fatigue Laboratory and described by Robinson (1). The exercise tests consisted of 1) a moderate fixed task, walking for 15 minutes on a motor-driven treadmill set at 3.5 miles per hour and at an 8.6 per cent grade, and 2) a maximal task, running up the same grade at a speed of 6 or 7 miles an hour, a speed designed to bring about exhaustion in 2 to 5 minutes. Data secured during the walk include heart rate changes recorded on a cardiometer during the 15-minute walk and for 10 minutes afterward, rates of respiration, lung ventilation and oxygen consumption during the 'steady state' (8-14 min.), and blood pressures determined by the auscultatory method with a mercury manometer during the first 10 minutes of recovery following the walk. Blood samples drawn at approximately the twelfth minute of the walk were analyzed for blood lactate and sugar and for plasma phosphorus and total nitrogen. Data secured during the running test aimed to measure the maximum metabolic, respiratory and circulatory adjustments of which the individual was capable and the rate at which each adjustment was made. Blood pressure measurements were again taken for 10 minutes following the run. Blood samples drawn 5 to 10

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minutes after the run were analyzed for blood lactate and sugar and for plasma phosphorus and total nitrogen.

The tests on the treadmill were preceded by a period of rest (up to  $2\frac{1}{2}$  hours), during which the subject lay on a comfortable bed while the following tests for baseline values were made: measurement of the lung volume and its subdivisions<sup>4</sup>, basal oxygen consumption by the closed circuit method<sup>4</sup>, determination of the blood and available fluid volumes (2), heart rate, blood pressure and rate of respiration, and drawing of an arterial blood sample for the determination of oxygen capacity and saturation, CO<sub>2</sub> content and combining power, blood sugar and lactate and plasma inorganic phosphorus and total nitrogen.

The tests included, in addition, a nutritional appraisal of the child according to the method of McCloy (3), with calculation of the index of build and index of weight. All of the tests were made in the morning with the subject fasting since the previous evening.

Methods used for analysis of the blood components reported were as follows: blood lactate by Edwards' modification (4) of the method of Friedemann, Cotonio and Shaffer (5), blood by the micro method of Folin (6), plasma inorganic phosphorus by the method of Fiske and Subbarow (7), and total nitrogen by the micro method of Pregl (8) as modified by Ma and Zuazaza (9), with subsequent calculation of total protein by subtracting an average value for non-protein nitrogen and multiplying by the factor 6.25.

#### SUBJECTS OF THE STUDY<sup>5</sup>

We have studied in this way 110 normal, healthy boys between the ages of 10 and 17 years. Figure 1 gives an anthropometric description of the boys in the form of frequency distribution charts for height, weight, index of build and index of weight. The averages for the age groups vary in weight from 140 cm. at 10 years to 172 cm. at 17 years, and in weight from 32 kg. at 11 years to 61 kg. at 17 years. The distributions of height and the indices of build and weight give evidence that the boys tested were fairly representative of the general population. The extremely thin or obese child was not included in this report. The age given in the charts for each group represents the average chronological age for the period covered by the group. Each group therefore includes boys one-half year younger or older than the age stated.

#### RESULTS

All responses to the tests showed wide variation within each age group, a large part of which would seem to be due to innate characteristics of the individual. Many of the results, however, appeared to follow a definite pattern with increasing age. The statistical significance of such patterns or variations was determined by analysis of variance. To aid in the analysis the mean and the frequency distribution of response to the several factors of the tests were plotted for each year of age as illustrated in figures 1 and 2. Inspection of these charts suggested the trend with age and the kind of statistical analysis to be made. In

<sup>4</sup> To be reported later.

<sup>5</sup> We wish to express our appreciation to the boys who participated in the study and to the University of Chicago Settlement House, the Valentine Boys Club, the Hyde Park Neighborhood House and the many friends who sent the boys to us.

some cases the trend represented a gradual change with increasing age. In those cases the analysis involved calculation of the significance of the regression coefficient and its standard error of estimate. For other factors tested the

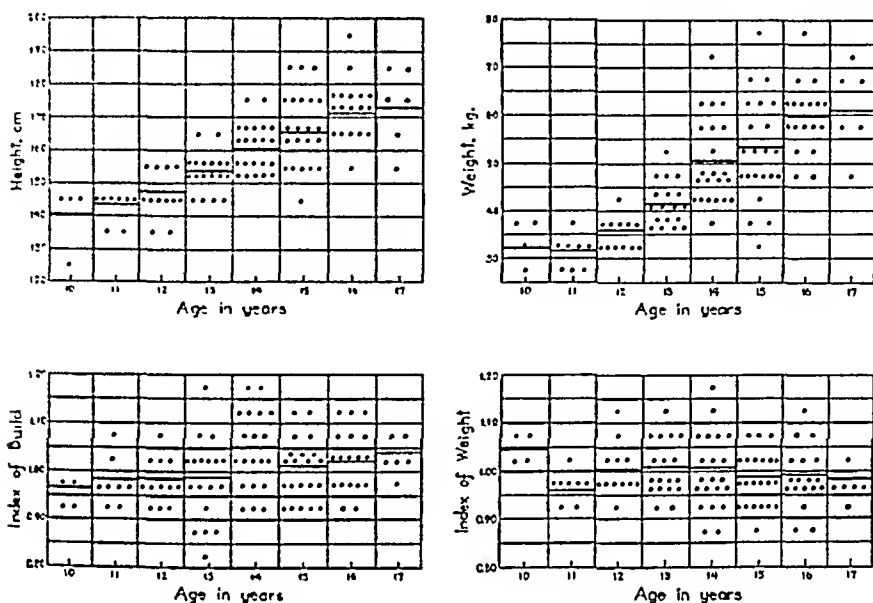


Fig. 1. AN ANTHROPOMETRIC DESCRIPTION of the boys included in this report, shown in the form of frequency distribution charts for height, weight and the indices of build and weight. The horizontal bars represent the mean for each age group.

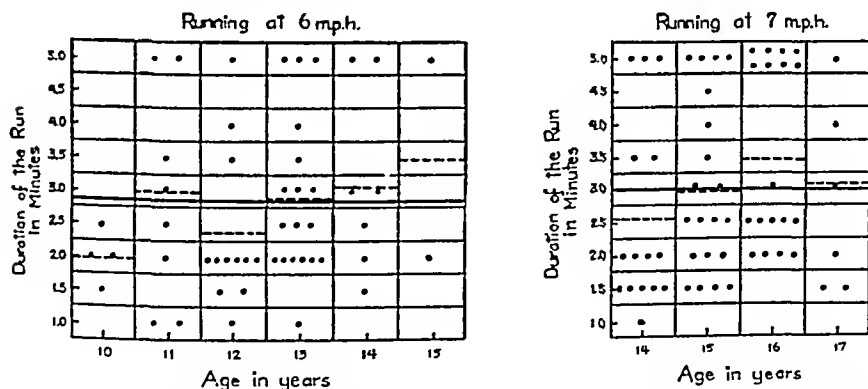


Fig. 2. RELATION OF THE AGE OF THE BOY TO his work capacity as measured by duration of grade running to exhaustion. The chart shows the frequency distribution, the mean for each group (broken lines) and the over-all mean at each speed (heavy solid line).

effect of age appeared as a rather abrupt shift in level at a certain age. When this was apparent the difference between the means of the two levels was tested for significance and the standard deviations of the distributions from the means were calculated.

TABLE 1. RESULTS OF A STATISTICAL ANALYSIS OF VARIANCE, TO SHOW THE EFFECT OF THE AGE OF THE BOY UPON HIS RESPIRATORY AND METABOLIC RESPONSES TO GRADE WALKING<sup>1</sup> AND RUNNING<sup>2</sup>

CONDITIONS	TIME OF EXERCISE, MIN.	AGE RANGE, YRS.	NO. IN GROUP	TYPE OF VARIATION <sup>3</sup> WITH AGE	'F' VALUE <sup>4</sup>	REGRESSION DATA		MEAN AND S.D. <sup>5</sup>
						EQUATION $Y = a + bx$	S.E. OF ESTIMATE <sup>6</sup>	
<i>Oxygen Consumption, ml/min/kg.</i>								
Recumbent		10-17	112	B	54.61 (3.94)	7.44 - 0.197x	±0.49	
Walking	8-14	10-17	107	B	15.75 (3.94)	31.6 - 0.350x	±1.64	
Running	0-0.5	10-13	38	B	5.10 (4.10)	35.6 - 1.28x	±3.35	16.8 ± 3.36
		14-17	66	A	0.48 (3.99)			39.7 ± 4.67
	0.5-1	10-17	105	A	0.31 (3.94)			46.9 ± 4.61
	1-2	10-17	99	A	0.61 (3.94)			45.8 ± 3.68
	2-3	11-13	17	C	8.15 (4.01)			49.1 ± 4.07
		14-17	40					46.4 ± 4.01
	3-4	11-13	10	A	2.00 (4.96)			
		14-17	24	B	6.62 (4.26)	19.3 + 2.11x	±3.79	49.8 ± 3.90
	4-5	11-17	24	A	3.82 (4.26)			47.8 ± 5.04
	Exhaustion	10-12	22	A	0.21 (4.30)			
		13-17	81	B	12.15 (3.96)	25.1 + 1.56x	±4.83	
<i>Respirations per Minute</i>								
Recumbent		10-17	108	B	3.76 (3.94)	21.6 - 0.34x	±3.12	
Walking	8-14	10-13	39	A	0.00 (4.09)			36.2 ± 5.35
		14-17	68	B	8.41 (3.98)	63.1 - 2.15x	±5.75	
Running	0-0.5	10-17	92	B	7.47 (3.95)	43.3 - 1.18x	±7.25	
	0.5-1	10-17	96	B	15.07 (3.94)	59.7 - 1.76x	±8.04	
	1-2	10-17	93	B	8.44 (3.95)	62.7 - 1.40x	±8.23	49.1 ± 5.69
	2-3	11-13	16	C	5.61 (4.49)			44.1 ± 7.55
		14-17	38					47.7 ± 7.42
	3-4	11-17	31	A	0.17 (4.16)			48.5 ± 7.66
	4-5	11-17	21	A	0.01 (4.32)			
	Exhaustion	10-17	99	B	5.03 (3.94)	60.5 - 0.92x	±7.26	
<i>Lung Ventilation, ml/min/kg.</i>								
Recumbent		10-12	22	C	11.81 (3.94)			199 ± 41
		13-17	84					158 ± 44
Walking	8-14	10-12	24	A	0.31 (4.26)			812 ± 97
		13-15	61	B	13.46 (3.93)	1259 - 37.4x	±84	650 ± 55
		16-17	24	A	0.03 (4.26)			
Running	0-0.5	10-17	106	B	20.46 (3.94)	974 - 29.9x	±120	
	0.5-1	10-17	105	B	11.67 (3.94)	1520 - 37.3x	±193	
	1-2	10-17	89	B	3.93 (3.95)	1761 - 22.9x	±191	1599 ± 161
	2-3	10-17	59	A	0.06 (4.00)			1698 ± 175
	3-4	11-17	53	A	1.42 (4.02)			1650 ± 214
	4-5	11-17	25	A	0.96 (4.24)			1602 ± 219
	Exhaustion	10-17	87	A	0.10 (3.95)			
<i>'True O<sub>2</sub>', %</i>								
Recumbent		10-13	39	B	5.12 (4.08)	0.23 + 0.263x	±0.686	3.65 ± 0.884
		13-17	85	A	0.95 (3.95)			
Walking	8-14	10-13	41	A	0.00 (4.08)			4.30 ± 0.387
		13-17	85	B	41.3 (3.96)	1.71 + 0.198x	±0.349	

TABLE I—*Concluded.*

CONDITIONS	TIME OF EXERCISE, MIN.	AGE RANGE, YRS.	NO. IN GROUP	TYPE OF VARIATION WITH AGE	't' VALUE <sup>1</sup>	REGRESSION DATA		MEAN AND S.D. <sup>7</sup>	
						EQUATION $Y = a + bx^1$	S.E. OF ESTIMATE <sup>4</sup>		
True O <sub>2</sub> %—Continued									
Running	0-0.5	10-14	67	A	0.38 (3.00)	$1.40 + 0.174x$	$\pm 0.527$	$3.90 \pm 0.528$	
		14-17	68	B	7.04 (3.05)				
	0.5-1	10-14	62	A	0.32 (4.00)			$4.81 \pm 0.573$	
		14-17	60	B	6.80 (3.08)				
	1-2	10-17	105	B	7.61 (3.04)	$2.82 + 0.095x$	$\pm 0.610$	$3.57 \pm 0.450$	
	2-3	11-13	18	C	5.31 (3.08)			$3.86 \pm 0.485$	
		14-17	40			$3.53 \pm 0.444$			
	3-4	11-13	10	C	3.05 (4.05)	$3.78 \pm 0.428$			
		14-17	27			$3.76 \pm 0.358$			
	4-5	11-17	26	A	0.00 (4.22)	$3.73 \pm 0.464$			
	Exhaustion	10-17	105	A	0.78 (3.04)				
Tidal Air+Vital Capacity									
Recumbent		10-12	23	C	8.71 (3.03)			$0.181 \pm 0.029$	
		13-17	85					$0.153 \pm 0.042$	
Walking	8-14	10-17	108	A	1.27 (3.04)			$0.353 \pm 0.068$	
Running	0-0.5	10-17	88	A	0.03 (3.05)			$0.328 \pm 0.083$	
	0.5-1	10-17	96	A	1.60 (3.04)			$0.450 \pm 0.089$	
	1-2	10-11	9	C	3.14 (3.05)			$0.475 \pm 0.093$	
		12-17	82					$0.520 \pm 0.070$	
	2-3	11-17	54	A	0.34 (4.02)	$0.261 + 0.010x$	$\pm 0.057$	$0.525 \pm 0.063$	
	3-4	11-17	31	B	7.76 (4.16)				
	4-5	11-17	23	B	6.63 (4.28)				
	Exhaustion	10-11	10	C	0.27 (3.04)			$0.475 \pm 0.094$	
		12-17	85			$0.123 + 0.027x$	$\pm 0.074$	$0.547 \pm 0.067$	
	Respiratory Quotient								
	Walking	8-14	10-13	41	B	7.04 (4.08)	$0.503 + 0.023x$	$\pm 0.056$	$0.884 \pm 0.044$
		14-17	68	A	0.25 (3.08)				
Running	0-0.5	10-17	107	A	0.32 (3.04)			$0.834 \pm 0.090$	
	0.5-1	10-17	108	A	1.85 (3.04)			$0.788 \pm 0.081$	
	1-2	10-12	21	C	3.68 (3.04)			$0.978 \pm 0.090$	
		13-17	85					$1.024 \pm 0.099$	
	2-3	10-12	9	C	1.94 (3.08)			$1.050 \pm 0.071$	
		13-17	58					$1.103 \pm 0.111$	
	3-4	10-12	4					$1.025$	
		13-17	35	A	0.04 (4.12)			$1.104 \pm 0.089$	
	4-5	13-17	24	B	9.46 (4.26)	$0.582 + 0.031x$	$\pm 0.075$	$1.010 \pm 0.089$	
	Exhaustion	10-12	22	C	18.66 (3.04)			$1.114 \pm 0.101$	
		13-17	84						
	Mechanical Efficiency								
Walking	8-14	10-17	106	A	0.12 (3.04)			$17.7 \pm 1.44$	

<sup>1</sup> Walking at 3.5 miles/hr., 8.6 % grade.<sup>2</sup> Running at 6.0 or 7.0 miles/hr., depending on the age and size of the boy, 8.6% grade.<sup>3</sup> Types of variation which appear to describe the relation of the age of the child to the results of the tests. A. No significant variation in the age groups specified. B. Linear regression to include the age groups specified. C. Significant variation between age groups, no significant regression within the age groups specified.<sup>4</sup> Values in parentheses represent Fisher's 5% level of confidence.<sup>5</sup> Y represents the variable under consideration; x, the age of the boy.<sup>6</sup> Standard error of estimate =  $\sqrt{\frac{\sum(y - Y)^2}{N - 2}}$ , where Y represents the value calculated from the regression equation,

N the number of individuals in the group.

<sup>7</sup> Standard deviation of distribution =  $\sqrt{\frac{\sum(x - m)^2}{N - 1}}$ , where m represents the mean of the group, N the number of individuals in the group.

The results of the statistical analyses are summarized in the tables and charts. In selecting the form of variation which best represented any given relationship to age, a certain amount of personal judgment was required. In a few cases a relationship or a difference between age groups which did not prove to be statistically significant has been treated as such, either because of a consistent variation within a time series, or to correlate it with related data. Comparison of related data reveals discrepancies when one set of values is derived from another by calculation. This occurs, for example, when absolute values

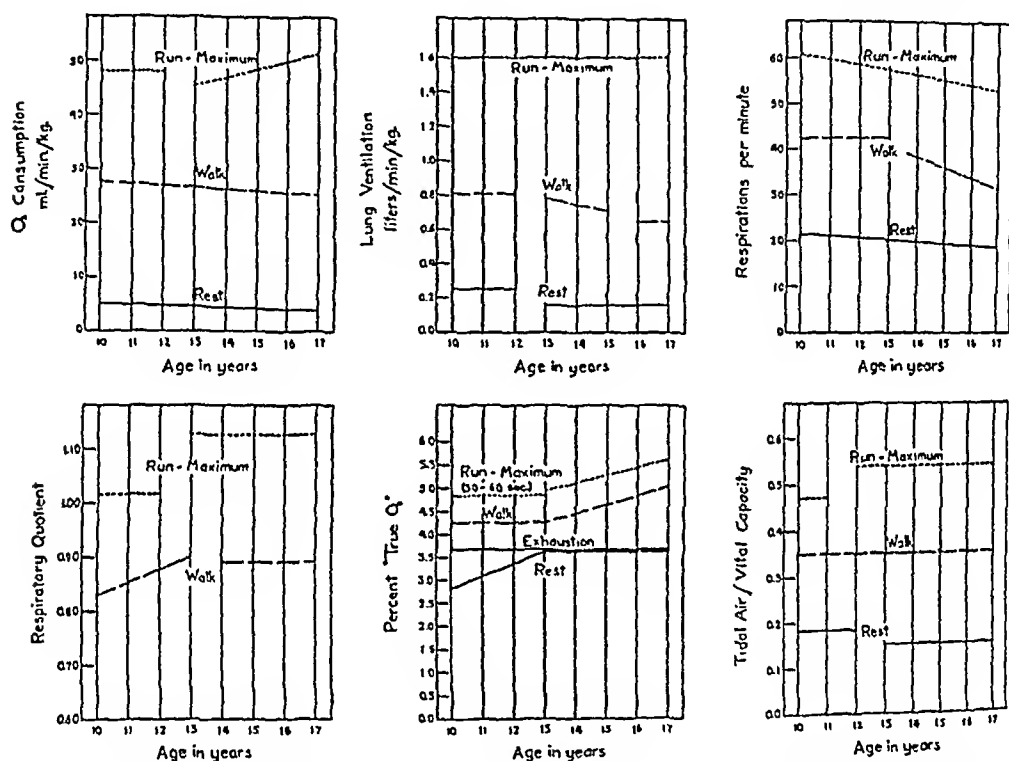


Fig. 3. RESPIRATORY AND METABOLIC RESPONSES to grade walking and running in relation to the age of the boy.

are compared with increments in response to work. It is also found when comparing trends in pulse pressure with trends in systolic and diastolic levels. In the case of discrepancies we believe truer relationships are expressed by trends derived from values in which the individual was compared with himself rather than by comparing one over-all trend with another.

*Physiological Responses to Grade Walking.* The moderate task of walking for 15 minutes on a motor-driven treadmill, at an 8.6 per cent grade and at 3.5 miles per hour was accomplished easily by all boys. Oxygen consumption during the steady state decreased with increasing age from a mean of 28.1 ml/min/kg. at 10 years to 25.7 ml/min/kg. at 17 years. Since the basal oxygen consumption showed a similar trend, from 5.47 to 4.09 ml/min/kg. during the same years, the average gain in oxygen consumption required for walking

varied little with age. The mechanical efficiency of walking showed no variation of statistical significance with age. The over-all mean efficiency of 17.7 per cent is slightly higher than Robinson's averages (1) for groups covering this age range. The value may have been influenced by the fact that many of the boys of this study were active in athletics at school or in boys' clubs.

The respiratory minute volume per unit of body weight showed little variation from 10 to 12 years but decreased progressively from 12 to 16 years. Since the ratio of tidal air to vital capacity remained close to 0.35 for all of the age

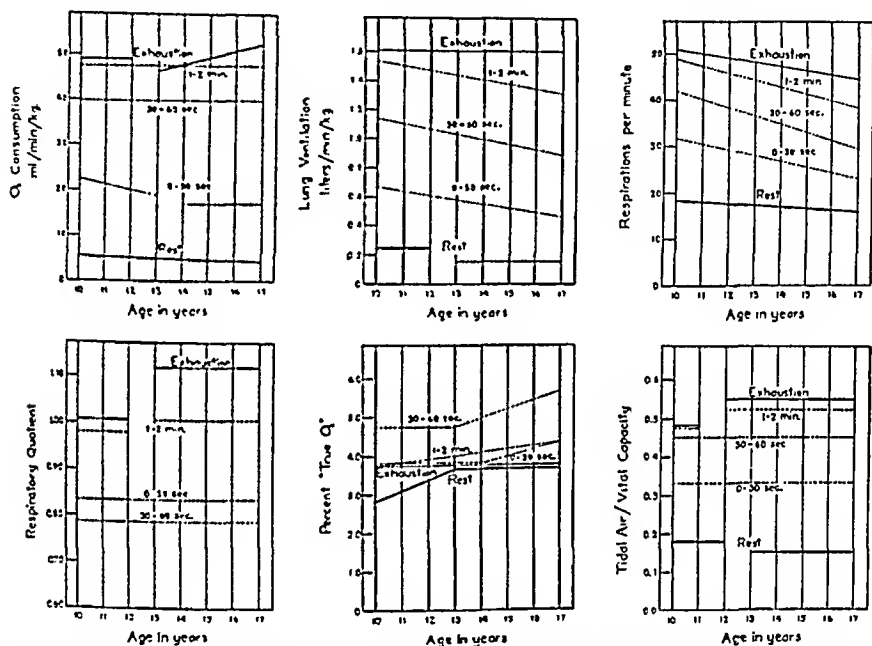


Fig. 4. RELATION OF THE AGE OF THE BOY to the speed of adjustment of the respiratory and metabolic mechanisms to supply energy for maximal effort (grade running).

groups, the decreased rate of lung ventilation in the older boys was related almost entirely to the decrease in respiratory rate which began at 14 years. As the respiratory rate decreased, the rate of utilization of the oxygen of the inspired air, the so-called 'true  $O_2$ ', increased from a mean of 4.30 per cent at 10 to 13 years to 5.09 per cent at 17 years. The respiratory quotient of the steady state increased from 0.83 to 0.89 as age increased from 10 to 13 years, but remained at an average level of 0.88 from 14 to 17 years. The rise in respiratory quotient from 10 to 13 years occurred during the years when the respiratory rate, lung ventilation per unit of body weight and 'true  $O_2$ ' remained at a constant level.

Lactic acid levels in blood samples drawn during the steady state showed an average increase of 53 per cent above the resting level, but there was no



significant variation in the lactate levels with age, nor was there a significant correlation between blood lactate concentrations and the respiratory quotient during the walk. Blood sugar levels during the steady state of the walk varied

TABLE 2. RESULTS OF A STATISTICAL ANALYSIS OF VARIANCE TO SHOW THE EFFECT OF THE AGE OF THE BOY UPON THE RESPONSE OF SOME OF THE BLOOD COMPONENTS TO GRADE WALKING AND RUNNING<sup>1</sup>

CONDITIONS	AGE RANGE, YRS.	NO. IN GROUP	TYPE OF VARIATION WITH AGE	'F' VALUE	REGRESSION DATA		MEAN AND S.D.
					EQUATION $Y = a + bx$	S.E. OF ESTIMATE	
<i>Blood Lactic Acid, mg/100 ml.</i>							
Recumbent	10-17	110	A	0.00 (3.94)			14.0 ± 4.97
During the walk	10-17	87	A	1.94 (3.95)			21.4 ± 5.25
After the run	10-11	6	A				
	12-17	80	B	12.41 (3.96)	$-10.10 + 5.00x$	±17.02	63.3 ± 25.63
<i>Blood Sugar, mg/100 ml.</i>							
Recumbent	10-17	92	A	0.10 (3.95)			99.2 ± 7.42
During the walk	10-17	84	A	0.00 (3.96)			98.1 ± 8.18
After the run	10-12	11	A	0.14 (4.84)			
	13-15	52	B	4.85 (4.03)	$32.3 + 5.92x$	±14.91	115.1 ± 9.30
	15-17	44	A	0.00 (4.06)			120.0 ± 16.15
<i>Plasma Protein, gm/100 ml.</i>							
Recumbent	10-17	110	A	2.03 (3.94)			6.96 ± 0.359
During the walk	10-17	85	A	1.45 (3.96)			7.66 ± 0.344
After the run	10-12	11	C	5.98 (3.95)			7.60 ± 0.325
	13-17	77					7.91 ± 0.404
<i>Plasma Inorganic Phosphorus, mg/100 ml.</i>							
Recumbent	10-13	36	B	5.55 (4.12)	$2.18 + 0.196x$	±0.487	
	13-17	89	B	11.54 (3.95)	$6.84 - 0.171x$	±0.593	
During the walk	10-11	7	A				
	12-17	78	B	8.39 (3.97)	$6.88 - 0.136x$	±0.537	4.96 ± 0.461
After the run	10-12	12	B	7.11 (4.84)	$-0.37 + 0.485x$	±0.522	
	12-14	37	B	4.37 (4.11)	$8.74 - 0.273x$	±0.595	
	14-17	62	A	0.00 (4.00)			4.90 ± 0.577

<sup>1</sup> Explanations are given in the footnotes below table 1.

from the individual resting levels by as much as ± 15 per cent, but the overall average for the walk was not significantly different from the average resting level. There was no significant variation in blood sugar levels with age from 10 to 17 years, either in the resting state or during the walk.

The inorganic phosphorus concentration of the plasma of samples drawn during the basal state rose from a mean of 4.14 mg/100 ml. at 10 years to 4.72 mg/100 ml. at 13 years, thence declined to a mean of 3.92 mg/100 ml. at 17

years. Blood samples drawn during the steady state of the walk had higher phosphorus concentrations in the plasma than corresponding samples drawn in the basal state, but with peak levels, 5.2 mg/100 ml., at 12 years instead of 13 years. The increase in concentration during the walk was on the average 20 per cent above the resting level in boys of 10 to 12 years, but only 11 per cent

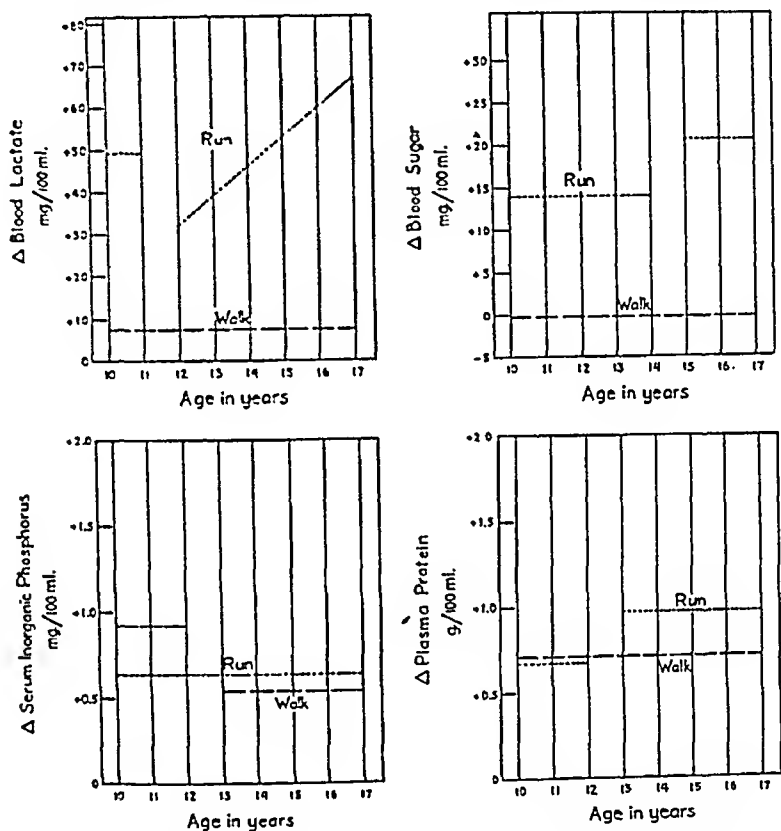


Fig. 5. RESPONSES OF SOME OF THE BLOOD COMPONENTS to grade walking and running in relation to the age of the boy.

above that level in those of 13 to 17 years. The difference is statistically significant at the one per cent level of confidence ( $F = 7.37$ ). Although a rise in plasma phosphorus concentration occurred during exercise in the majority of boys studied, 9 boys out of 88 tested showed either no rise or a slight decrease from the resting level. These were all in the 13 to 17-year-age group.

Plasma protein concentrations showed no significant variation with age in blood samples drawn during the basal state, and no significant over-all trend with age during the steady state of the walk. However, a difference between the means of 7.41 and 7.73 gm/100 ml. for the 10 to 12- and 13 to 14-year-old groups respectively is statistically significant at the 5 per cent level of confi-

dence ( $F = 6.67$ ). Plasma protein concentrations during the steady state of the walk were on the average 10.5 per cent higher than the resting level. The older boys had a greater range of response with values 2.5 to 20 per cent above the resting level as compared with values 5 to 15 per cent above that level in boys of 10 to 12 years.

The heart rate was recorded in the sitting and standing position as well as in the recumbent position during the pre-exercise rest period in order to secure base line values for comparison with working and recovery levels. Whether recumbent, sitting or standing, the resting heart rate averages for the age groups remained quite constant from 10 to 12 years but decreased progressively thereafter to 16 years. The age group averages suggest that a greater decrease occurred between 15 and 16 years than at any other time.

Mean heart rates for the age groups while walking in the steady state varied in much the same way as the resting levels and, as a consequence, the rise of the heart rate above the standing level showed little variation with age. Boys of 12 to 14 years, however, had a slightly higher increase in heart rate during the walk than did the younger and older boys, with an average increment of 66 beats/minute as compared with 60 and 59 beats/minute in the younger and older groups respectively. In the case of the younger boys this difference is not statistically significant because of the wide variation and the comparatively few boys studied, but the difference between the boys of 12 to 14 and those of 15 to 16 years is significant at the 5 per cent level ( $F = 4.06$ ).

There is little evidence in table 3 and figure 6 that age from 10 to 17 years influenced the speed with which the heart increased its rate in response to moderate work. In order to determine whether an effect of age had been masked by expressing the data as trend lines, the acceleration of heart rate response was calculated for each individual and averaged for the age groups. For this purpose the total response of the heart rate to grade walking was defined as the difference between the heart rate in the last minute of the walk and the pre-exercise rate in the standing position. On this basis the average percentage of completion of response at a given time interval for individuals of the same age varied slightly with age, from 41 to 54 per cent after 15 seconds, from 53 to 60 per cent after 30 seconds, from 71 to 82 per cent after 1 minute, and from 84 to 92 per cent after 5 minutes of walking. The value at 15 seconds included the anticipatory rise which occurred a few seconds before the walk began. At all time intervals the 14-year-old group showed the highest percentage of completion of response. Tests for significance gave  $F$  values of 3.09, 4.01, 1.05, 0.60 and 0.97 for differences between the means of the 13- and 14-year-olds after 15, 30, 45, 60 and 120 seconds of walking, and  $F$  values of 2.71, 5.31, 3.67, 2.58 and 2.92 for corresponding differences between the means of the 14- and 15-year-olds. These values are questionably significant. It would seem quite possible that the faster acceleration of heart rate shown by the 14

TABLE 3. RESULTS OF A STATISTICAL ANALYSIS OF VARIANCE, TO SHOW THE EFFECT OF THE AGE OF THE BOY UPON THE HEART RATE RESPONSE TO GRADE WALKING AND RUNNING<sup>1</sup>

CONDITIONS	TIME OF EXERCISE OR REST, MIN.	AGE RANGE, YRS.	NO. IN GROUP	TYPE OF VARIATION WITH AGE	F VALUE	REGRESSION DATA		MEAN AND S.D.
						EQUATION $Y = a + bx$	S.E. OF ESTIMATE	
Recumbent		10-12	24	A	1.36 (4.26)			72.5 ± 9.4
		12-17	94	B	5.70 (3.95)	93.7 - 1.72x	±10.1	
Sitting		10-12	20	A	0.33 (4.35)			90.0 ± 9.7
		12-17	64	B	12.97 (3.99)	131.5 - 3.44x	±11.2	
Standing		10-12	20	A	1.36 (4.35)			100.0 ± 9.2
		12-17	63	B	5.70 (3.99)	125.5 - 2.20x	±10.8	
Walking	0.25	10-12	19	A	0.57 (4.38)			128.7 ± 13.8
		12-17	64	B	9.37 (3.99)	167.4 - 3.13x	±11.2	
	0.50	10-12	19	A	1.89 (4.38)			136.6 ± 9.0
		12-17	64	B	14.34 (3.99)	178.6 - 3.41x	±10.7	
	0.75	10-12	18	A	0.42 (4.41)			142.2 ± 9.6
		12-17	62	B	17.64 (4.00)	198.6 - 4.36x	±11.7	
	1	10-13	31	A	0.03 (4.17)			145.6 ± 10.9
		13-17	54	B	9.44 (4.02)	199.4 - 4.11x	±10.8	
	2	10-12	20	A	0.00 (4.35)			152.0 ± 12.8
		12-17	64	B	16.33 (3.99)	205.6 - 4.38x	±12.7	
	3	10-12	20	A	0.02 (4.35)			151.0 ± 11.2
		12-17	64	B	14.62 (3.99)	203.9 - 4.24x	±13.0	
	4	10-12	20	A	0.03 (4.35)			152.0 ± 12.0
		12-17	64	B	20.90 (3.99)	211.3 - 4.67x	±11.9	
	5	10-12	20	A	0.00 (4.35)			155.0 ± 12.3
		12-17	64	B	11.61 (3.99)	202.4 - 3.83x	±13.1	
	10	10-13	32	A	0.17 (4.15)			160.9 ± 13.3
		13-17	54	B	12.19 (4.02)	225.6 - 4.97x	±12.4	
	15	10-12	20	A	0.03 (4.35)			165.0 ± 14.5
		13-17	64	B	11.40 (3.99)	213.1 - 3.95x	±13.7	
Resting after the walk	0.25	10-12	19	B	1.30 (4.38)	96.3 + 4.65x	±14.0	
		13-16	50	B	7.60 (4.03)	224.4 - 5.55x	±15.4	
	0.5	10-12	19	B	1.92 (4.38)	60.2 + 6.61x	±16.6	
		12-16	60	B	8.77 (4.00)	195.2 - 4.72x	±15.9	
	0.75	10-12	19	B	0.85 (4.38)	75.0 + 4.00x	±15.1	
		12-16	61	B	5.86 (4.00)	163.6 - 3.46x	±15.5	
	1	10-12	19	B	0.34 (4.38)	92.6 + 2.30x	±13.7	
		12-16	61	B	9.40 (4.00)	166.3 - 3.82x	±13.8	
	2	10-12	19	A	0.11 (4.38)			112.4 ± 11.4
		12-16	60	B	6.16 (4.00)	146.1 - 2.81x	±12.1	
	3	10-16	72	B	3.66 (3.98)	127.2 - 1.54x	±12.6	
	4	10-16	71	B	10.78 (3.98)	126.4 - 1.75x	±8.2	
	5	10-16	71	B	4.63 (3.98)	121.9 - 1.59x	±11.4	
	10	10-16	70	B	1.62 (3.98)	109.6 - 0.93x	±10.7	
	0.25	10-11	8					146.2 ± 8.5
		12-14	32	C	5.74 (4.09)			156.7 ± 11.5
		15-17	29	C	2.77 (4.20)			151.5 ± 13.1
	0.5	10-11	8					167.1 ± 7.4
		12-14	31	C	2.43 (4.10)			172.4 ± 8.7
		15-17	28	C	7.35 (4.21)			165.5 ± 11.7

TABLE 3—Concluded

CONDITIONS	TIME OF EXERCISE OR REST, MIN.	AGE RANGE, YRS.	NO. IN GROUP	TYPE OF VARIATION WITH AGE	F VALUE	REGRESSION DATA		MEAN AND S.D.
						EQUATION $Y = a + bx$	S.E. OF ESTIMATE	
Running	0.75	10-11	7					173.5 ± 8.5
		12-14	32	C	3.10 (4.10)			179.7 ± 8.4
		15-17	28	C	5.08 (4.21)			175.2 ± 9.6
	1	10-11	7					178.9 ± 10.3
		12-14	32	C	3.46 (4.10)			184.7 ± 7.5
		15-17	28	C	5.14 (4.21)			180.2 ± 9.5
	2	10-13	29	A	0.01 (4.18)			192.3 ± 6.7
		14-16	37	B	4.29 (4.11)	245.2 - 3.66x	±8.3	
	3	10-12	6	A	0.76 (5.99)			192.5 ± 10.0
		13-16	28	B	11.95 (4.21)	222.6 - 1.95x	±4.0	
At exhaustion	0.25 0.5	10-17	70	A	0.12 (3.98)			195.6 ± 7.1
		10-17	70	A	0.02 (3.98)			185.4 ± 9.5
		10-12	19	B	0.52 (4.41)	188.0 - 1.98x	±9.6	
		12-17	61	B	2.06 (4.00)	151.4 + 1.40x	±11.2	
Resting after the run	0.75	10-12	19	B	1.07 (4.41)	189.9 - 3.94x	±13.2	
		12-17	62	B	8.09 (4.00)	99.8 + 3.84x	±15.5	
	1	10-12	19	B	2.95 (4.41)	232.2 - 8.91x	±18.1	
		12-17	63	B	9.86 (4.00)	67.1 + 5.12x	±18.9	
	2	10-17	71	A	0.32 (3.98)			120.0 ± 14.3
	3	10-17	71	A	0.12 (3.98)			112.7 ± 11.4
	4	10-17	71	A	0.02 (3.98)			110.5 ± 11.3
	5	10-17	71	A	0.00 (3.98)			109.5 ± 10.4
	10	10-17	70	A	0.32 (3.98)			106.9 ± 9.7

<sup>1</sup> Explanations are given in the footnotes below table 1.

year old group is a chance phenomenon of sampling. There were no other consistent variations between the age group averages.

In a similar manner individual recovery rates after the walk were calculated by expressing the decrease in heart rate from the working level at various time intervals as per cents of the total difference between the heart rate at the end of the walk and the pre-exercise value in the sitting position. Averages for the age groups showed 12 to 20 per cent recovery in 15 seconds, 38 to 44 per cent in 30 seconds, 59 to 63 per cent in one minute, 64 to 70 per cent in 2 minutes, 71 to 81 per cent in 5 minutes and 76 to 86 per cent in 10 minutes. For the first 2 minutes after the walk there were no consistent variations in rates of recovery with age, but from the 3rd to the 10th minute after the walk boys of 12, 13 and 14 years showed higher percentages of recovery than either the younger or the older boys. Heart rates were not recorded longer than ten

minutes. The differences between the mean recoveries of the 12 to 14- and 15 to 16-year-old-boys at the 3rd, 5th and 10th minute after the walk, 6.6, 7.3 and 6.8 per cent units respectively, are statistically significant ( $F = 4.62, 8.97$  and  $6.23$  respectively). Differences between the means of the 12 to 14- and 10 to 11-year-old boys of 3.3, 7.8 and 5.2 per cent respectively for like time

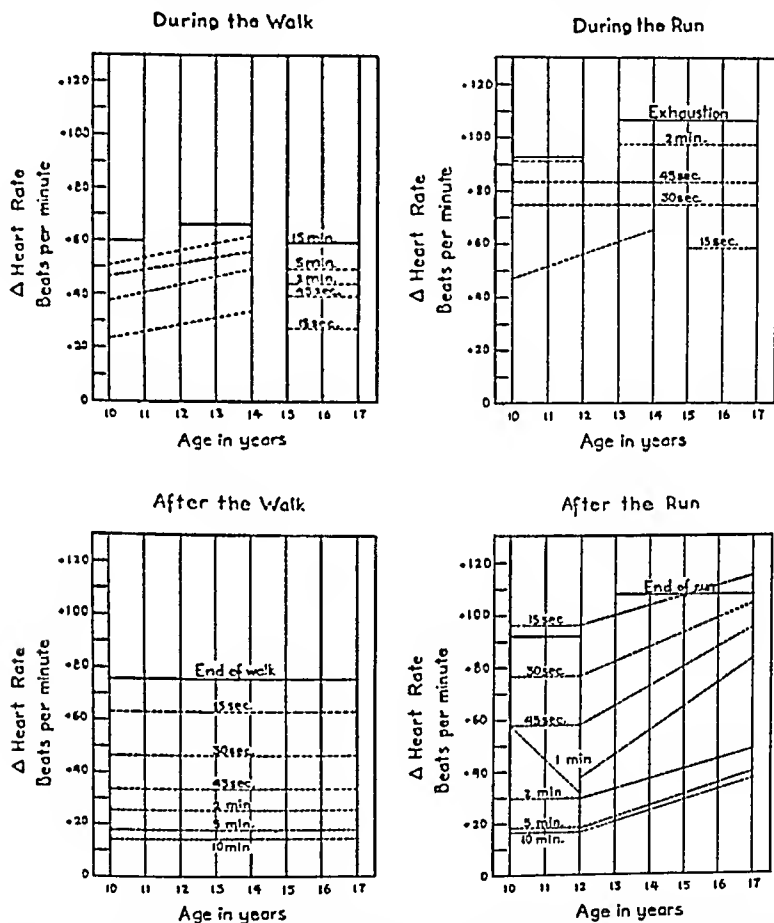


Fig. 6. RESPONSES OF THE HEART RATE to grade walking and running in relation to the age of the boy. Responses are expressed in terms of deviations from the pre-exercise heart rate level measured in the same posture.

intervals after the walk are less significant ( $F = 0.57, 4.53,$  and  $2.53$  respectively).

Blood pressures were determined in the recumbent position before exercise and in the sitting position during the first 10 minutes following exercise. In the basal state there was little variation in the diastolic level with age. There was also little variation with age in the systolic and pulse pressure levels of the younger boys while in the basal state, but boys of 15 to 17 years had slightly

TABLE 4. RESULTS OF A STATISTICAL ANALYSIS OF VARIANCE, TO SHOW THE EFFECT OF THE AGE OF THE BOY UPON THE BLOOD PRESSURE RESPONSE TO GRADE WALKING AND RUNNING<sup>1</sup>

CONDITIONS	TIME AFTER EXER- CISE, MIN.	AGE RANGE, YRS.	NO. IN GROUP	TYPE OF VARIA- TION WITH AGE	'F' VALUE	' REGRESSION DATA		MEAN AND S.D.	
Systolic Pressure, mm. Hg									
Recumbent		10-12 13-17	22 80	A B	0.46 (4.30) 21.26 (3.97)	39.6 + 4.82x	±11.1	105.0 ± 8.0	
Rest after walk	1	10-11	9	C	2.03 (4.12)	60.8 + 4.86x	±13.6	116.1 ± 7.8	
		12-13	27					124.6 ± 17.2	
		14-16	59	B	4.81 (4.01)				
		17	6					130.0	
	2	10-11	10	C	1.00 (4.11)	56.5 + 4.25x	±10.5	109.0 ± 5.2	
		12-13	27					114.9 ± 15.0	
		14-16	60	B	6.35 (4.01)				
		17	6					115.0	
	3	10-11	10	C	0.76 (4.11)	51.7 + 4.18x	±11.6	104.0 ± 7.4	
		12-13	27					108.0 ± 13.5	
		14-16	60	B	5.07 (4.01)				
		17	6					113.3	
	4	10-11	10	C	1.44 (4.11)	80.5 + 2.25x	±11.3	102.0 ± 4.8	
		12-13	27					106.5 ± 11.3	
		14-16	60	B	1.53 (4.01)				
		17	6					113.3	
	5	10-11	10	C	1.03 (4.13)	69.2 + 2.90x	±11.6	100.0 ± 7.1	
		12-13	25					103.8 ± 10.9	
		14-16	60	B	2.42 (4.01)				
		17	6					111.7	
	10	10-11	10	C	0.61 (4.12)	38.8 + 4.77x	±11.0	97.7 ± 9.2	
		12-13	26					100.0 ± 10.7	
		14-16	60	B	7.33 (4.00)				
		17	6					108.3	
Rest after run	1	10-11	10	C	3.61 (4.10)	17.4 + 9.24x	±17.3	132.0 ± 7.9	
		12-13	29					141.4 ± 14.8	
		14-16	59	B	11.12 (4.01)				
		17	5					158.2	
	2	10-11	11	C	1.44 (4.09)	50.2 + 6.44x	±15.7	123.4 ± 7.0	
		12-13	29					127.5 ± 12.0	
		14-16	59	B	6.33 (4.01)				
		17	5					153.2	
	3	10-13	40	B	2.81 (4.09)	80.1 + 3.12x	±11.8	151.8	
		14-16	59	B	3.03 (4.01)				±14.8
		17	5						
	4	10-13	40	B	4.16 (4.09)	72.3 + 3.21x	±9.9	141.2	
		14-16	59	B	1.75 (4.01)				±13.5
		17	5						
	5	10-13	40	B	3.37 (4.09)	67.0 + 3.22x	±11.1	133.0	
		14-16	58	B	2.48 (4.01)				±13.9
		17	6						
	10	10-13	37	B	1.06 (4.11)	75.9 + 2.08x	±11.9	110.8	
		14-16	58	B	6.21 (4.01)				±10.9
		17	5						
	Diastolic Pressure, mm. Hg								
	Recumbent		10-17	100	A	1.22 (3.94)			71.1 ± 9.1
	Rest after walk	1	10-12	21	A	0.33 (4.32)	21.7 + 3.48x	±12.9	68.8 ± 13.2
			13-17	80	B	8.46 (3.96)			72.7 ± 11.1
2		10-17	22	A	0.00 (4.30)	37.3 + 2.51x	±10.6		
		13-17	81	B	7.16 (3.96)				

TABLE 4—Concluded.

CONDITIONS	TIME AFTER EXER- CISE, MIN.	AGE RANGE, YRS.	NO. IN GROUP	TYPE OF VARIA- TION WITH AGE	't' VALUE	REGRESSION DATA		MEAN AND S.D.			
						EQUATION $Y = a + bx$	S.E. OF ESTI- MATE				
Diastolic Pressure, mm. Hg—Continued											
	3	10-12	22	A	0.57 (4.30)	$38.5 + 2.64x$	$\pm 10.6$	72.7 $\pm$ 10.2			
		13-17	80	B	7.22 (3.06)						
	4	10-14	57	C	6.44 (3.04)			75.0 $\pm$ 9.6			
		15-17	44					70.8 $\pm$ 9.0			
	5	10-14	57	C	8.31 (3.04)			74.1 $\pm$ 9.5			
		15-17	45					70.4 $\pm$ 8.9			
	10	10-14	57	C	13.12 (3.04)			72.2 $\pm$ 8.4			
		15-17	45					78.0 $\pm$ 7.9			
	Rest after run	1	10-17	100	A			0.31 (3.04)			68.5 $\pm$ 15.2
		2	10-17	105	A			0.52 (3.04)			67.4 $\pm$ 12.0
3		10-17	104	A	0.65 (3.04)			69.2 $\pm$ 11.6			
4		10-17	106	A	0.75 (3.04)			69.7 $\pm$ 12.7			
5		10-17	106	A	1.05 (3.04)			71.8 $\pm$ 11.3			
10		10-17	100	A	1.24 (3.04)			73.0 $\pm$ 8.2			
Pulse Pressure, mm. Hg											
Recumbent		10-14	57	C	4.62 (3.04)			37.6 $\pm$ 8.4			
		15-17	43					41.3 $\pm$ 8.5			
Rest after walk	1	10-12	21	C	3.82 (3.04)			51.4 $\pm$ 13.4			
		13-17	80					59.3 $\pm$ 17.2			
	2	10-12	22	C	3.09 (3.04)			39.1 $\pm$ 11.0			
		13-17	81					44.3 $\pm$ 12.5			
	3	10-12	22	C	2.05 (3.04)			34.1 $\pm$ 11.0			
		13-17	81					38.0 $\pm$ 12.4			
	4	10-13	37	C	9.16 (3.04)			29.9 $\pm$ 9.3			
		14-17	65					36.2 $\pm$ 10.7			
	5	10-13	36	C	7.24 (3.04)			27.8 $\pm$ 8.5			
		14-17	66					35.7 $\pm$ 11.0			
Rest after run	10	10-13	36	C	11.37 (3.04)			28.3 $\pm$ 6.9			
		14-17	66					34.9 $\pm$ 9.7			
	1	10-12	21	A	0.10 (4.32)	$-18.2 + 7.34x$	$\pm 21.8$	69.5 $\pm$ 15.0			
		12-16	86	B	16.26 (3.06)			92.2			
		17	5					51.8 $\pm$ 10.8			
	2	10-11	11	A	0.13 (4.84)	$-17.9 + 6.38x$	$\pm 19.4$	86.2			
		12-16	87	B	16.23 (3.06)			42.5 $\pm$ 10.0			
		17	5					81.2			
	3	10-11	11	A	0.98 (4.84)	$-42.8 + 7.48x$	$\pm 17.6$	39.2 $\pm$ 10.1			
		12-16	88	B	21.55 (3.08)			67.0			
	17	5			33.3 $\pm$ 8.9						
4	10-12	23	A	0.09 (4.28)	$-7.5 + 4.32x$	$\pm 16.7$	50.3 $\pm$ 17.2				
	13-16	88	B	11.33 (3.05)			54.8				
	17	5					28.3 $\pm$ 8.6				
5	10-12	23	A	0.24 (4.28)	$-70.1 + 8.50x$	$\pm 14.9$	35.2				
	12-14	50	B	10.21 (4.03)							
	14-16	60	A	0.02 (4.00)							
	17	5									
10	10-12	12	A	0.01 (4.75)	$-10.5 + 3.19x$	$\pm 10.0$					
	12-16	84	B	15.05 (3.06)							
	17	5									

<sup>1</sup> Explanations are given in the footnotes below table 1.

but significantly higher levels. A rather large proportion of the 13 year olds, 7 out of 15, had systolic pressures under 95 mm. This would seem to be an



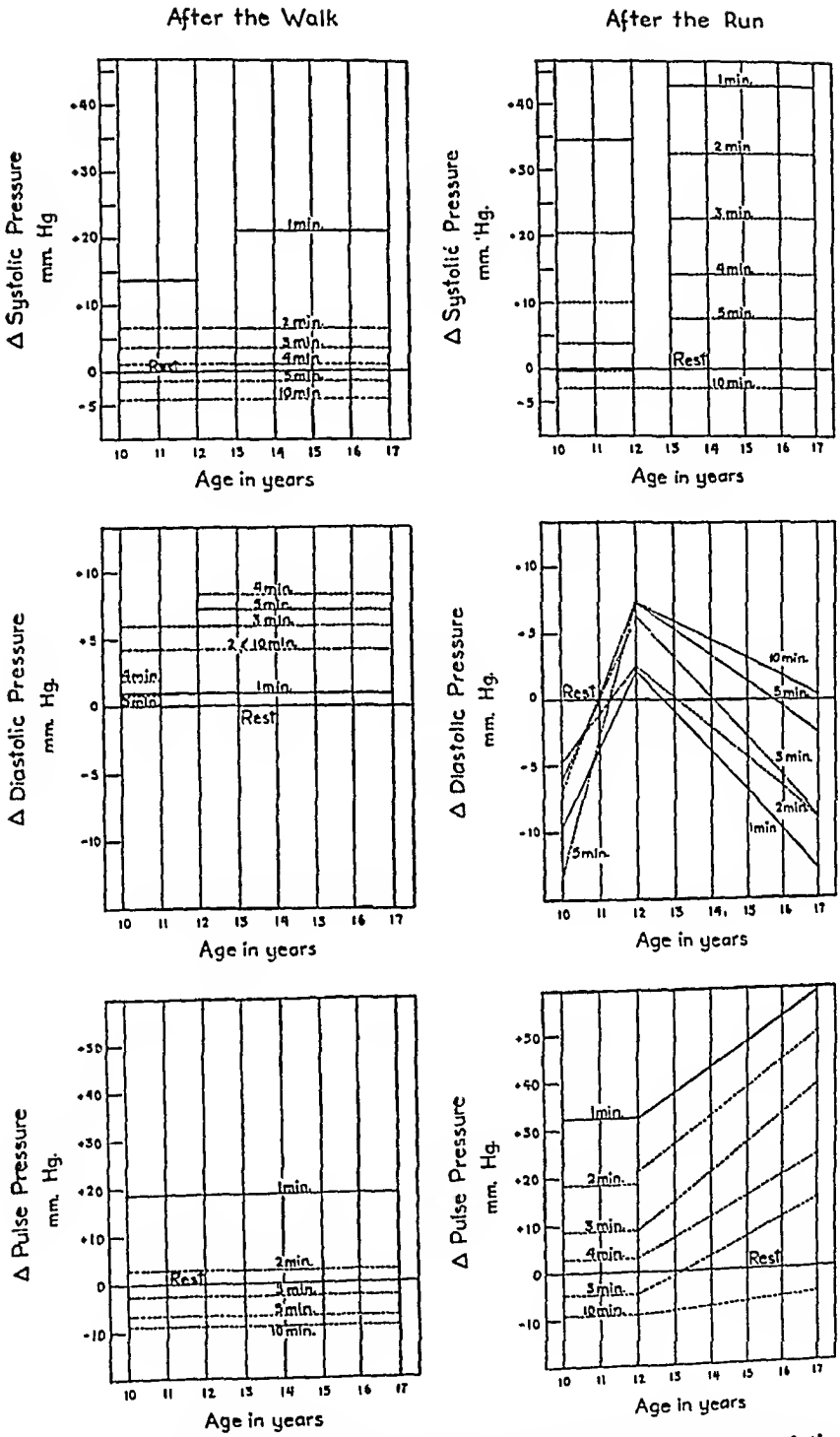


Fig. 7. RESPONSES OF THE BLOOD PRESSURE to grade walking and running in relation to age of the boy. Blood pressures are expressed in terms of deviations from the pre-exercise levels.

accident of sampling rather than a characteristic of the particular age. There is no evidence of such a depression of systolic levels at 13 years in studies which have recorded resting blood pressures of large numbers of children (10-17).

Systolic pressures one minute after the walk were on the average 18.5 and 24.9 mm. above the pre-exercise level in boys of 10 to 12 and 13 to 17 years respectively. These levels fell rapidly in the next minute, then more slowly, to reach the resting level in all age groups approximately 4 minutes after exercise had ceased. Subsequently, systolic pressures often continued to fall and were still an average of 5 mm. below the pre-exercise level when the measurements were discontinued after 10 minutes of rest. While the systolic pressures were falling, the diastolic pressures usually rose, especially in the older boys, in such a way as to reduce the pulse pressure to the resting level in approximately 2 minutes. With the continued fall in systolic level, the pulse pressure also fell, occasionally to very low levels and remained approximately 10 mm. below the resting level, regardless of age, for at least 10 minutes after the walk.

*Physiological Responses to Running.* The treadmill was set at the same grade for all tests, 8.6 per cent, and at a speed of 6 or 7 miles per hour, depending on the age and size of the boy. In general boys of 10 to 13 years ran at 6 m.p.h. and boys of 14 years and older at 7 m.p.h. The average durations of the run at 6 and at 7 m.p.h. were nearly the same, 2.8 and 3.0 minutes respectively (fig. 2). Under these conditions the older group accomplished more work per unit of body weight chiefly because of greater speed. In general the average duration of the run at a given speed increased with age but such a trend has not been proven statistically because of the great differences in individual capacity in every group. Undoubtedly all of the boys did not push themselves to the same state of exhaustion, and some had not reached the limit of their capacity in 5 minutes of running at 7 m.p.h. For this reason the duration of the run did not always give an accurate measure of the capacity of the individual boy for running. This limitation must be kept in mind when maximal values are discussed. The term 'maximal' as used here represents the maximum attained in the tests under the influence of moderate urging on the part of the director. It may sometimes fall short of the true maximum.

The maximal rate of oxygen consumption attained per unit of body weight during the run varied with age. It was lowest in the 13-year-old boys, an average of 44.8 ml/min/kg. This level rose gradually with age to an average of 50.9 ml/min/kg. at 17 years. The younger boys of 10 to 12 years averaged 48.2 ml/min/kg. The maximal intakes of this study are slightly below those found by Robinson (1) which were 52.1, 47.1, and 52.8 ml/min/kg. for boys averaging 10.5, 14.1 and 17.4 years of age respectively, but the variation with age is in the same direction.

Maximal respiratory minute volume per unit of body weight showed no variation related to the age of the boy. In the older boys it was attained with fewer respirations by increasing the ratio of tidal air to vital capacity. Acceleration to maximal rates of lung ventilation and respiration occurred more

slowly in the older boys. In the first two minutes of the run the lower respiratory minute volume per unit of body weight in the older boys was balanced by greater utilization of the oxygen of the inspired air in such a way that after the first half minute their capacity for oxygen consumption kept pace with the younger boys. In the first half minute of the run oxygen consumption increased more rapidly in the younger boys.

A higher R.Q. at exhaustion in the older boys appeared first at 13 years. It would seem to be related to metabolic factors associated with lactic-acid formation. Blood-lactate levels at exhaustion were higher in the older boys whereas their respiratory rates were lower.

Average blood-sugar concentrations for the age groups in samples drawn after the run were higher in boys of 15 and 16 years (123 and 119 mg/100 ml. respectively) and lower in boys of 13 and 17 years (109 and 110 mg/100 ml. respectively) than in the other age groups. Values higher than 135 mg/100 ml. were found in 7 boys of 15 to 16 years as compared with only one such case in boys under 15 years. Robinson (1) found the same relationship between blood-sugar concentrations after exhausting exercise and age, but with averages about 10 mg. higher. We have the impression, difficult to prove, that the higher blood-sugar concentrations were found in those boys who pushed themselves farther toward exhaustion. It is quite possible that Robinson was more successful than we were in getting the boys to put themselves out in effort. Blood-sugar concentrations after the run showed no relationship to corresponding lactic-acid levels.

In many cases plasma inorganic phosphorus concentrations were elevated to much the same degree both during the walk and after the run. In 30 per cent of the cases, however, chiefly in boys of 14 years and younger, the plasma phosphorus concentrations were slightly lower after the run than during the walk, whereas in 46 per cent of the cases, chiefly in boys of 15 to 17 years, they were higher after the run. As in the walk, plasma phosphorus concentrations were highest in the 12-year-old boys.

Although plasma protein concentrations showed little variation with age during the walk, they were definitely higher in the older boys after the run with a mean concentration of 7.91 g/100 ml. at 13 to 17 years as compared with 7.60 g/100 ml. at 10 to 12 years. In the latter age groups plasma protein concentrations were much the same during the walk and after the run.

Maximum heart rate levels during the run varied little with age from the over-all average of 196 beats/minute. Age group averages increased from 193 beats/minute at 12 years to 198 beats/minute at 14 years, thence decreased to 193 beats/minute at 16 years, but the slight trends toward and away from a maximum at 14 years were not statistically significant ( $F = 3.52$  and  $2.40$  respectively). The difference between the maximum heart rate level and the

resting level in the standing position was greater in boys of 13 to 17 years than in boys of 10 to 12 years.

The data of table 3 would suggest that the acceleration of the heart rate to reach the maximum was slower in boys of 10 and 11 years than in boys of 12 to 14 years. Percentage of completion of the response at 15, 30 and 45 seconds was calculated in the same manner as during the walk. Averages for 10 to 11, 12 to 14 and 15 to 16 years showed 53.4, 60.9 and 57.1 per cent of the maximum response reached at 15 seconds, 73.0, 76.7 and 72.8 per cent at 30 seconds, and 80.6, 85.0 and 81.6 per cent at 45 seconds respectively, but the differences between the age group averages were not statistically significant.

The return of the heart rate to the resting level after the run was faster in the younger boys. Slower deceleration began at 13 years and became increasingly marked as the age of the boy increased from 13 to 16 years. After one minute of rest recovery was 60.7 per cent complete on the average in the 12-year-old, 47.1 per cent complete in the 13-year-old, and 39.8 per cent complete in the 16-year-old. After 5 minutes of rest percentage recovery varied on the average from 83.3 per cent at 12 years to 69.9 per cent at 16 years. Similarly, after 10 minutes of rest average percentage recoveries decreased from 84.6 per cent at 12 years to 74.1 per cent at 16 years. Too few boys of 10, 11 and 17 years were studied to justify statements concerning those ages.

Systolic blood pressures one minute after the run were more markedly elevated in the older boys, with levels which averaged 43 mm. above the resting level as compared with 34 mm. in boys of 10 to 12 years. After the first minute the systolic level fell rather slowly, reaching the resting level in about 5 minutes in the younger boys, somewhat later in the older ones.

The diastolic level one minute after the run was on the average approximately the same as the resting level in the case of the 12 to 14-year-old boys but was lower than the resting level in all other age groups. Inter-individual variations of response were great, ranging from 52 mm. below to 24 mm. above the pre-exercise level. The age trends during recovery (fig. 7) show that the diastolic level tended to rise slowly after exercise. Actually, during the recovery period, diastolic pressures followed several different patterns. In 35 per cent of the boys studied minimum diastolic pressures were observed in the first few measurements after the run, after which the level rose slowly toward the resting level. In the older boys of 15 to 17 years an even greater proportion, 43 to 50 per cent, showed this type of response. In 23 per cent of the boys the minimum diastolic level was reached later, from 2 to 5 minutes after cessation of exercise. In 10 per cent of the boys diastolic pressures which were initially high after the run decreased to the pre-exercise level during the 10-minute recovery period. The remaining 32 per cent showed no appreciable change in diastolic pressure during the recovery period in spite of the fact that approxi-

mately half of these had post-exercise levels higher than the resting levels. The various patterns of diastolic response to exercise have been represented diagrammatically by Shock (18) as the resultant of varying time and intensity of two vascular responses, dilation followed by constriction.

The pulse pressure one minute after the run showed a minimum rise averaging 33 mm. in boys of 11 and 12 and a maximum rise averaging 56 mm. in the 16-year-old boys. Recovery was more rapid in the younger boys in whom the pre-exercise level was reached on the average in  $4\frac{1}{2}$  minutes, whereas the resting level was not reached until some minutes later in boys of 14 to 17 years. As was the case after the walk, the pulse pressure continued to fall below the pre-exercise level and remained at approximately 6 mm. below that level for at least 10 minutes after exercise in all age groups except the 10-year-olds.

#### DISCUSSION

Since the present study has been concerned with the effect of age on the physiological responses of the child to exercise, little attention has been paid to resting levels except as they served as base line values from which responses to work were calculated. The resting levels would seem to deserve brief comment, however, concerning their relation to the body economy. It would appear from the results of this study that as a boy passes through the adolescent period the physiology of his resting state changes in the direction of the sparing of energy. Per unit of body weight or surface, the over-all requirement for oxygen to maintain life in the basal state decreases. Respiratory rate, ratio of tidal air to vital capacity, respiratory minute volume per unit of body weight decrease, accompanied by an increase in utilization of the oxygen of the inspired air, decrease in heart rate and elevation of systolic blood pressure.

Trends in resting values with age are reflected in similar trends in the working values of the steady state of the walk and, in the case of oxygen consumption and the circulatory responses, are an important cause of such trends. Thus, although oxygen consumption and heart rate recorded in the steady state decrease, and pulse pressure measured within one minute after the walk increases with the increasing age of the boy, the increments of oxygen consumption, heart rate and pulse pressure in response to moderate work vary little with age from 10 to 17 years. At this age level the mechanical efficiency of walking also does not seem to be influenced by the age of the boy.

The rise in the respiratory quotient of the steady state with increasing age from 10 to 13 years, unaccompanied by changes in respiratory rate, lung ventilation per unit of body weight and per cent 'true'  $O_2$ , and unrelated to variations in blood lactate levels, gives further weight to the suggestion of Robinson (1) that the supply of carbohydrates for fuel is diminished in the younger boys. According to Robinson it is possible that the younger boys possess less carbohydrate reserves as a result of the 15-hour fast which pre-

ceded the tests. Dill, Edwards and D Meio (19) found that the R.Q. in work tends to decrease as reserves of carbohydrates are depleted but that the blood-sugar levels are unaffected unless carbohydrate stores are considerably depleted. The present data show no evidence of an influence of age upon the blood-sugar levels either in rest or during moderate work in the years from 10 to 17.

The average blood-lactate level of 21.5 mg/100 ml. which was found during the steady state of the walk approximates that found by Robinson (1) in boys of the same age (21 mg/100 ml. at 10.5 years to 17 mg/100 ml. at 17.4 years), but the resting level in the boys of our study was slightly higher, 14 mg/100 ml. as compared with 11 mg/100 ml. Our data gave no evidence of variation in the blood-lactate level of the steady state with increasing age from 10 to 17 years. It is questionable whether the slight decrease apparent in Robinson's data is significant. The presence in the blood of a lactate concentration that is approximately 50 per cent higher in the steady state of the walk than during rest offers a problem that is not yet completely solved. It represents the resultant of several factors, rate of formation in the tissues, rate of diffusion from the tissues to the blood and rate of removal, either in the tissues directly or from the blood.

Contrary to the older view that lactic acid in the blood reaches an equilibrium concentration during the steady state of sub-maximal work, the results of Bang (20) and of Crescitelli and Taylor (21) show that blood-lactate concentration often reaches a maximum before the end of the work period after which it begins to decline. According to Bang's conception lactic acid in moderate exercise accumulates in the tissues in the first few minutes of exercise only, while adjustments are being made to supply adequate oxygen to the tissues for the aerobic metabolism of exercise. Blood-lactate concentrations at a given time interval during the walk may therefore represent the maximum for some individuals, but in others it may be less than the maximum, either because removal is progressing at a faster rate than diffusion from accumulated stores, or because the maximum concentration has not yet been reached. Margaria, Edwards and Dill (22) have shown, too, that the blood-lactate concentration is not proportional to the oxygen debt and that the oxygen debt after moderate exercise may be due entirely to an 'alactacid' mechanism.

There seems to be no reason to suppose from these findings that the blood-lactate concentration toward the end of the walk can be used as a measure of the oxygen debt or as a measure of rate of adaptation to meet oxygen needs. Nevertheless, evidence suggests that the blood-lactate concentration during moderate exercise bears some relation to physical fitness. Crescitelli and Taylor (21) report that less fit individuals give a significantly greater blood-lactate concentration throughout the entire period of submaximal exercise. Bang (20) has shown that the blood-lactate concentration during the exercise

period is lowered by training. Margaria, Edwards and Dill (22) have found that the lactate concentration may not rise above the resting level until a critical level of oxygen consumption is reached which, in the well-trained individual, may represent a comparatively severe grade of work.

On the basis of training one would expect that the older boys might show less of a rise in blood-lactate concentration during moderate exercise. Since there is no evidence of such an effect one must suppose either that daily activity does not constitute training for grade-walking on the treadmill or, what seems more likely, that the maximum concentration is reached earlier in the younger boys because of their more rapid adjustments to supply oxygen and that at the time the sample was drawn lactate concentrations had decreased to levels similar to the lower maximal levels of the older boys. Although the rate of adaptation to meet oxygen needs has not been measured during moderate exercise, the fact that the acceleration of oxygen uptake to meet maximal demands takes place more rapidly for the first 30 seconds in the younger boys suggests that this is also the case under conditions of moderate work. Without question more information could be gained by following the time course of the blood-lactate curve during exercise.

A trend toward higher plasma protein levels in the older boys during the steady state of the walk suggests that the fluid balance between plasma and extracellular spaces may be subjected to greater hydrostatic forces in the older boys. This conception is in agreement with the pulse pressures, which were 21 mm. above the resting level in boys of 13 to 17 years as compared with 14 mm. in 10 to 12-year-old boys when measured within one minute after exercise.

The increase in plasma inorganic phosphorus concentration during rest, which reached a maximum at about 13 years, and the subsequent decrease throughout adolescence is apparent also in the data of Stearns and Warweg (23). Previously the decline from childhood values to those of the adult had been described as occurring at 19 years (24, 25). The rise in plasma phosphorus concentration as the result of exercise was first described by Havard and Reay (25) and has been reported by a number of investigators since then (26-31). In a study of the effects of 15 minutes of moderate exercise on the bicycle ergometer (32) we found an increase of 0.62 mg/100 ml. in boys averaging 14 years as compared with a rise of 0.37 mg/100 ml. in boys averaging 17 years. In the present study, with a different type of moderate exercise, boys of 10 to 12 years showed an average rise of 0.93 mg/100 ml. as compared with 0.54 mg/100 ml. in boys of 13 to 17 years.

The meaning of the increase in plasma inorganic phosphorus concentration during exercise is not clear. It has been thought to represent diffusion of inorganic phosphorus away from the working muscles where it is known to exist in higher concentration during work, but the reports of Irving and Bostedo (33) and of Bollman and Flock (34) raise doubt as to the possibility of diffusion

of phosphate ions through the muscle cell walls during activity. Our inability to detect any increase in inorganic phosphorus in the serum of blood samples immediately after exercise in dogs (35) suggests that there may be a species difference. Interpretation of the age differences observed both during rest and moderate exercise must await further study.

Age group averages suggest that the capacity for running increases progressively from 12 to 16 years but this is not proven statistically because of the great variation in capacity among boys of the same age group. Because of the conditions set for running, the increased capacity of the older boys appears in this study chiefly as capacity for maintaining greater speed. Judged by maximal oxygen consumption and blood lactate concentrations after the run, the greater capacity of the older boys for running would appear to be linked with greater capacity for supplying both aerobic and anaerobic energy.

Maximal capacity for oxygen consumption was lowest in boys of 13 years, and highest in boys of 17 years when referred to a unit of body weight. The relatively low oxygen capacity of the 13-year-old boys is also evident in Robinson's data (1) in the group averaging 14.1 years. The increasing capacity for oxygen consumption with increasing age from 13 to 17 years is not surprising. In addition to growth effects, it could be attributed in large measure to effects of training in boys who are active physically, especially in those who have engaged in athletics. The decreased capacity for oxygen consumption in the 13-year-old boys as compared with the younger boys is not so easily understood. It is characteristic of these boys from the second minute to the end of the run. It does not seem to be related to capacity for running, for the 13-year-old boys ran longer on the average than those of 10 to 12 years, and presumably without expenditure of more anaerobic energy since blood-lactate levels were not higher. Their decreased oxygen consumption is associated with decreased utilization of the oxygen of the inspired air rather than with lower rates of lung ventilation. This suggests the influence of circulatory or metabolic factors rather than respiratory factors. Evidence points against the influence of circulatory factors since the heart rate accelerated just as rapidly in the 13-year-olds as in the younger boys and attained the same maximum. Pulse pressures measured within the first minute after the run also were no lower. It may be possible that the oxygen requirement for a given output of energy by the muscles may be lower in the 13-year-olds than in the younger children, because of the influence of hormonal factors associated with puberty.

The maximal capacity for heart rate and for lung ventilation per unit of body weight varies little with age from 10 to 17 years, but greater reserves and increased capacity for running are secured in the older boy by the greater differential between maximal and resting levels. In the older boys maximal respiratory minute volume is attained more slowly and with fewer respirations.



The trends and the means for given age groups agree fairly well with averages reported by Robinson (1) for the 10-, 14-, and 17-year-old groups.

The greater capacity for running shown by boys 14 to 17 years old is associated, not with greater oxygen consumption during the first two minutes of the run, but rather with the capacity to increase that consumption still further by raising the rates of respiration and ventilation up to levels reached much earlier by the younger boys. Linked with this is the ability to utilize a greater percentage of the oxygen that passes through the lungs early in the run. The greater capacity to utilize oxygen may be due partly to the greater differential between the resting and the maximal heart rates in the older boys but perhaps in greater part to a capacity for increased circulation of blood through the lungs because of larger stroke volume. Unfortunately, the stroke volume could not be measured in this study but some indication is obtained from the rise in pulse pressure which increased consistently with increasing ages from 12 to 17 years. The increment of pulse pressure over the resting level averaged 55.7 mm. in 16-year-old boys as compared with 32.7 mm. in boys of 10 to 12 years. It would be important also to know whether or not a greater arterio-venous difference played a part in increasing the oxygen utilization in the lungs of the older boys. This could not be determined in the present study.

*In addition to higher blood-lactate concentrations, the older boys are characterized by certain other changes in the composition of the blood in response to the maximal stress of running up-grade to exhaustion. Those changes apparent in the present study are a) higher blood-sugar concentrations in boys of 15 and 16 years; b) higher plasma protein concentrations in boys of 13 to 17 years; and c) plasma inorganic phosphorus concentrations in boys of 15 to 17 years, which unlike those of the younger boys, tend to be higher than corresponding values during the walk. The significance of these differences is not clear. From the data available it is impossible to know to what extent concentrations may have been affected by the previous work and subsequent recovery period and by the 5 to 10 minutes of rest between the end of the run and the drawing of the blood sample, nor to what extent the apparent effect of age may be dependent upon the fact that many of the older boys ran longer. It seems possible that at least some of the differences can be attributed to a capacity of the older boys to drive themselves farther toward exhaustion.*

It seems pertinent to consider to what extent the results of this study reliably represent trends in the general population of boys of this age. Figure 1 has shown that the boys are fairly representative as regards height, weight and build. They represent a mixture of national origins with Polish predominating. Since many of them were contacted through boys' clubs, they may have been more active in athletics and sports than the average boy of the general population. Due to the nature of the tests it was impossible to secure ideal sampling

and to follow the individual boy serially. The number of boys of 10 to 12 years included in this study is rather small for a statistical analysis. Any apparent lack of trend during those years does not mean that a trend does not exist but that individual variations are so large that for small numbers no trend can be detected that has statistical significance. For these several reasons we believe that while the trends presented in this study are highly suggestive of trends in the general population of boys, further study involving more ideal sampling and a serial study of the individual boy over a period of years would establish these trends more reliably or show where they are in error.

In addition to suggesting trends with age and relationships between physiological functions the data presented here have value in that the regressions and corresponding standard error of estimate, or in case of lack of trend, the means and the standard deviations of distribution from the mean, give an estimate of the range of normal variation of response to be expected at any given age and *offer reliable means of evaluating the performance of an individual child*. The use of such norms in an evaluation of functional fitness of children from the clinics will be discussed in a later report.

#### SUMMARY

The relation of age to the physiological responses of the older child (10-17 years) to both moderate and maximal work on a motor-driven treadmill has been studied by statistical analysis of the variance of response of 110 normal, healthy boys. Moderate exercise consisted in walking 15 minutes at 3.5 miles per hour and maximal exercise of running to exhaustion at a speed of 6 or 7 miles per hour, with the treadmill set at an 8.6 per cent grade.

The following responses showed significant variation with age at the 5 per cent level of confidence or better. During the steady state of the walk, rates of respiration and lung ventilation decreased with age from 14 to 17 years, 'true  $O_2$ ' and respiratory quotient increased from 10 to 13 years, plasma phosphorus concentration was higher in the younger boys of 10 to 12 years, and elevation of the heart rate above the resting level was higher and its deceleration after the walk was faster in boys of 12 to 14 years than in both younger and older boys. In the first half minute of the run, during the period of adjustment, oxygen consumption accelerated at a faster rate in the younger boys. During the first two minutes of the run the acceleration of respiratory rate and of lung ventilation relative to body weight was slower in the older boys but was accompanied by relatively greater utilization of the oxygen of the inspired air. At exhaustion, oxygen consumption showed minimum values at 13 years, then increased to a maximum at 17 years; the respiratory quotient reached higher levels in the older boys beginning at 13 years; elevation of the blood lactate concentration was at a minimum at 12 years, increased progressively

from 12 to 17 years; respiratory rates decreased with age from 10 to 17 years, while the ratio of tidal air to vital capacity reached higher levels beginning at 12 years; elevation of the heart rate above the resting level was higher in the older boys, beginning at 13 years; elevation of the pulse pressure increased with age from 12 to 17 years; blood sugar and plasma protein concentrations reached higher levels in the older boys, beginning at 15 years in the case of blood sugar and at 13 years in the case of plasma protein. During recovery from the run the heart rates and pulse pressures of boys of 10 to 12 years decelerated more quickly than in the older boys.

Responses which showed no significant variation with age were: a) during the steady state of the walk, net oxygen consumption and mechanical efficiency, ratio of tidal air to vital capacity, elevation of the pulse pressure above the resting level, blood lactate and sugar and plasma protein concentrations; b) rates of recovery of pulse pressure after the walk; and c) at exhaustion, heart rate, lung ventilation and per cent 'true  $O_2$ '.

The different responses and their variations with age have been interrelated and their relations to the body economy have been discussed. The value of the data in establishing the normal range of response in this age range, to which the responses of the individual child can be referred, has been emphasized.

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# Corneo-retinal Potential in Anoxia and Acapnia<sup>1</sup>

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THE CORNEO-RETINAL POTENTIAL was first used for the recording of eye movements in man by Fenn and Hursh (1). They placed electrodes just lateral to the eyes on each side of the head and recorded with a string galvanometer the potentials developed when the eyes were moved right or left. The results showed that the deflection obtained on the record was directly proportional to the sine of the angle of deviation of the eyes. The same phenomenon can now be used in reverse, i.e., by deviating the eyes right and left alternately to a constant degree and measuring the deflection of the galvanometer an estimate can be made of any changes in the corneo-retinal potential which may result from changes in the condition of the subject. It occurred to us that this potential might show characteristic changes in anoxia and acapnia and might even be useful as a physiological measure of the effect of low O<sub>2</sub> or low CO<sub>2</sub> on the body.

## METHOD

Electrodes were of the type used for brain-wave recording and consisted of a shallow cup attached to the skin with collodion. Through a hole in the cup, the underlying space was filled with electrode jelly. One of these electrodes was attached to each side of the head just lateral to the eyes. To provide points of fixation for the eyes, a wooden T was prepared, the top of which was 50 cm. in length and the upright 26 cm. In taking a record, the T was held horizontally with the base of the upright against the front of the oxygen mask, and the eyes were fixated alternately on two nails fixed at either end of the crossbar. The angle of deviation of the eyes was, therefore, about 45° to each side of the center. The string was used at a sensitivity of about 3 cm./m.v. A calibration deflection with the eyes fixated in the midline was recorded just before each record of eye movement so that all movements could be expressed in millivolts.

## RESULTS

*Anoxia.* These experiments were begun with the idea that the corneo-retinal potential (CRP) might vary with anoxia. To test this, 18 experiments were tried in which the CRP was recorded during decompression to 18, 20 or 23 thousand feet or during the inhalation of 9 per cent O<sub>2</sub> in N<sub>2</sub> at ground level.

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<sup>1</sup> This work was done under a contract recommended by the Committee on Medical Research between the University of Rochester and the Office of Scientific Research and Development.

The results of a preliminary series of 6 such experiments are shown in table 1. In this series only one record was taken at each altitude and the figures are not very reliable. On the average, however, there was a 16 per cent increase in the CRP with only one small decrease recorded.

TABLE 1. PRELIMINARY MEASUREMENTS OF THE EFFECT OF ANOXIA ON THE CORNEO-RETINAL POTENTIAL (CRP) (ONLY ONE RECORD FOR EACH FIGURE)

SUBJECT	DATE	ALTITUDE 10 <sup>3</sup> FT.	INSPIRED GAS	NORMAL CRP	MAXIMUM CRP	INCREASE
				<i>m. v.</i>	<i>m. v.</i>	%
M. A. E.....	1/3	40	O <sub>2</sub>	.36	.465	29
M. A. E.....	1/4	15	air	.48	.56	17
L. E. C.....	1/4	18	air	.85	.925	9
H. R.....	1/5	18	air	.427	.41	-4
L. E. C.....	1/5	18	air	.523	.567	8
V. G. S.....	1/5	(a) 15	air	.40	.56	31
		(b) 40	O <sub>2</sub>	.40	.50	25
Average.....				.49	.57	16

TABLE 2. EFFECT OF ANOXIA AND ACAPNIA ON THE CORNEO-RETINAL POTENTIAL

SUBJECT	DATE	ALTITUDE 10 <sup>3</sup> FT.	INSPIRED GAS	NORMAL CRP	MAXIMUM CRP	INCREASE
<i>Anoxia</i>						
				<i>m. v.</i>	<i>m. v.</i>	%
C. G. B.....	1/20	0	9%O <sub>2</sub>	.83	1.44	74
C. G. B.....	1/25	0	9%O <sub>2</sub>	.83	1.37	65
C. G. B.....	1/27	20	air	.70	1.19	70
C. G. B.....	3/3	0	9%O <sub>2</sub>	.95	1.14	20
C. G. B.....	3/11	(a) 18	air	1.09	1.34	23
		(b) 21	air	1.09	1.86	71
J. A. F.....	1/25	(a) 20	air	1.03	1.14	11
		(b) 23	air	1.03	1.55	50
J. A. F.....	2/10	18	air	.96	.99	1
M. A. E.....	1/27	20	air	1.10	1.31	19
M. A. E.....	2/10	18	air	.87	.81	-7
M. A. E.....	1/22	0	9%O <sub>2</sub>	.77	.74	-4
V. G. S.....	2/10	18	air	.74	.73	-1
R. G.....	3/11	18	air	1.09	1.05	-4

For each CRP measurement 3 or more records were measured and averaged. Except for subject C. G. B. and for J. A. F. at 23,000 feet, the increases in CRP are not impressive.

Subsequently, the electrodes were improved and tested for constancy in control experiments and records were taken at frequent intervals throughout the experiments. The results of 12 such experiments are given in table 2 on 5 different subjects. In this series, large increases in CRP averaging 54 per cent were regularly observed in one subject (C. G. B.) but only 2 of the

other 7 experiments showed any appreciable change. From this, it is evident that subjects vary markedly in their responses but anoxia has no effect except in a few cases. It seemed possible that these results might depend upon the

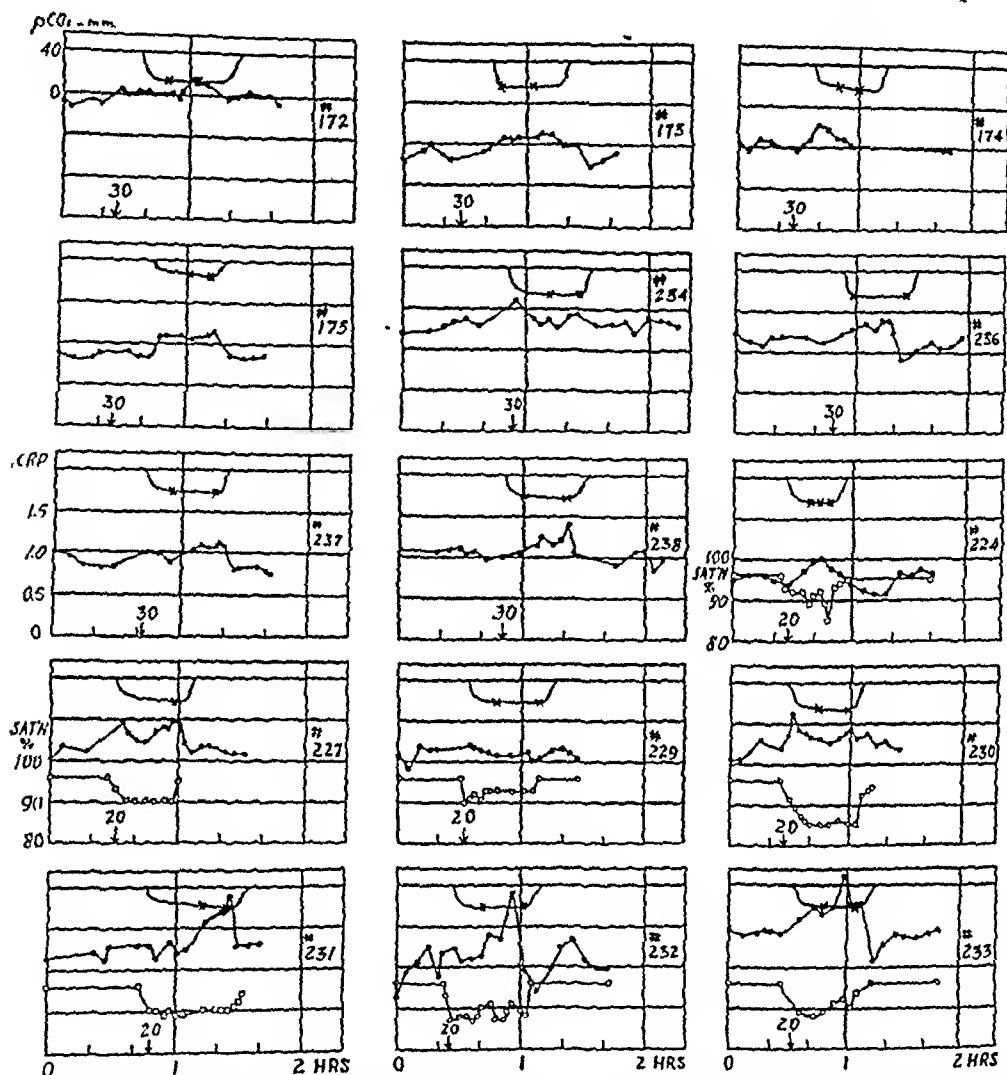


Fig. 1. CORNEO-RETINAL POTENTIALS before, during, and after hyperventilation on the pneumator. Time of arrival at altitude is indicated by an arrow in each chart. The altitude in thousands of feet was 30 or 20 as indicated by the figure over the arrow. The upper curve in each chart (crosses) is the alveolar  $\text{CO}_2$  tension, the middle curve (dots), the corneo-retinal potential, and the lower curve (open circles), the oximeter readings. In general the CRP goes up when the  $\text{pCO}_2$  goes down. The time of descent is indicated by the rise of the  $\text{pCO}_2$  curve. Groups of points were averaged together for the statistical study of table 5.

varying degrees of hyperventilation in different subjects under anoxic conditions. Indeed, all of the effects observed might be due to the acapnia which inevitably accompanies anoxia in varying degrees. Another series of experiments was, therefore, carried out. The results are shown in figure 1<sup>2</sup>. Two kinds of experiments are included: 1) acapnia alone and 2) acapnia with anoxia.

<sup>2</sup> Complete data of these experiments are given in table 3 of Part VII of our original report No. 410 to Committee on Aviation Medicine of the O.S.R.D. December 18, 1944 obtainable from the National Research Council, Washington, D.C.

For the acapnia alone, the subjects were taken to a simulated altitude of 30,000 feet breathing  $O_2$ . Records of CRP were taken at ground level and at altitude without hyperventilation. Then  $O_2$  was taken through the G.E. pneumolator set for a high ventilation rate and alveolar samples were taken at intervals in order to follow the  $pCO_2$  along with the CRP. After 20 to 30 minutes of hyperventilation, the chamber was brought back to ground level and recovery was followed breathing air for 20 to 30 minutes. The first 8 experiments in figure 1 (nos. 172-238) were of this type.

TABLE 3. ADDITIONAL EXPERIMENTS ON THE EFFECTS OF ACAPNIA WITHOUT ANOXIA

FLIGHT	SUBJECT	ALTITUDE	ALVEOLAR $pCO_2$	MEAN CRP	MEAN $\Delta$ CRP	DURATION	NO. OF TESTS
			mm. Hg	m. r.	m. r.	min.	
2/13	R. G.	GL	(40)	.90			3
		30 on $O_2$	24	.99	+.09	16	3
		30	21	1.00	+.10	32	2
		GL					
2/20	M. E.	GL	(40)	.98			3
		18 on $O_2$	20	1.12	+.14	17	2
		18	15	1.16	+.18	45	3
		GL	(40)	1.06	+.08	10	2
2/22	C. B.	GL	(40)	.93			3
		30 on $O_2$	18	1.25	+.32	10	3
		30	14	1.19	+.26	45	4
		GL	(40)	.87	-.06	20	1
2/24	C. B.	GL	(40)	.91		20	4
		GL	27	1.06	+.15	15	7
		GL	20	1.28	+.37	55	6
		GL	(40)	1.05	+.14	20	2
2/29	W. F.	GL	(40)	1.46			4
		GL	18.5	1.52	+.06	15	3
		GL	17	1.58	+.12	32	5
		GL	16	1.61	+.15	60	5
			(40)	1.58	+.12	28	1

For anoxic acapnia a similar procedure was followed except that the subject was taken to 20,000 feet breathing air through the pneumolator,<sup>3</sup> and no records were taken at altitude without hyperventilation. In these experiments the arterial saturation was also followed with a Millikan-Coleman oximeter. The next 7 experiments of figure 1 (224-233) were of this type. All these 15 experiments are plotted in figure 1 to show the time course of the changes in  $pCO_2$ , CRP, and saturation.

<sup>3</sup>The pneumolator is an apparatus built by the General Electric X-Ray Corporation which facilitates hyperventilation by providing positive pressure during inspiration and ambient pressure during expiration.



The 5 additional experiments in table 3 are similar to the first type in that they involved acapnia alone, but they differ in some details of procedure. Two of these experiments were done at ground level in air and one of them at 18,000 feet instead of 30,000 feet on  $O_2$ , but in all cases the pneumolator was used and there was no anoxia. In the statistical analysis these 5 experiments have not been treated as part of the series.

All the experiments in figure 1 and table 3 are represented in a mass plot in figure 2. Experiments at 20,000 feet with anoxia are plotted as solid circles while acapnia points without anoxia are plotted as empty circles. It is evident that all the points with or without anoxia fall within the same range showing an

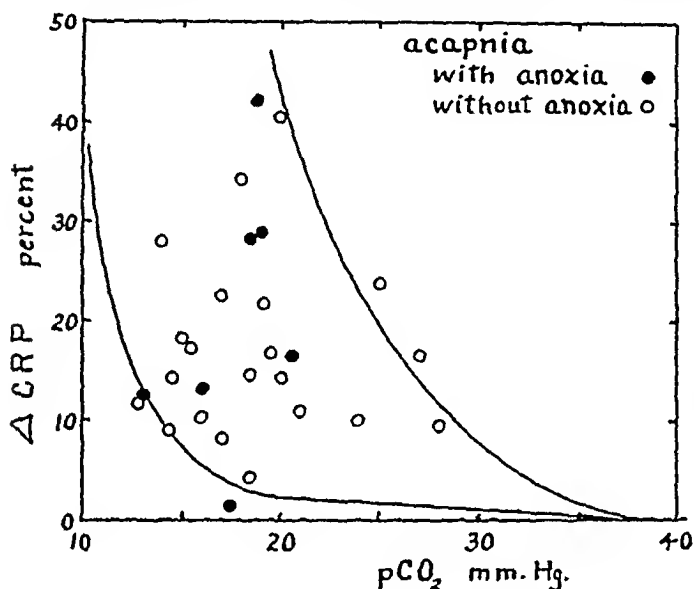


Fig. 2. PERCENTAGE CHANGES in the corneo-retinal potential (ordinates) at different levels of alveolar  $CO_2$  tension (abscissae) as compared to the ground level value at about 40 mm.  $pCO_2$ . Points with anoxia were run at 18,000 ft. breathing air and do not differ significantly from similar points without anoxia (open circles). The lines suggest the probable family of curves represented by the points.

increase in CRP with lowering of the  $pCO_2$  and none of the experiments indicates a fall in CRP. In the latter respect they are all surprisingly uniform although the scatter is very large.

Table 4 shows a comparison of acapnia with anoxic acapnia for 8 different subjects. The percentage increase in CRP is given for each condition together with the corresponding alveolar  $pCO_2$ . Inspection shows that for any one subject the  $pCO_2$  values are about the same for the two conditions (being, if anything, higher in anoxia) while the CRP increases are only a little higher in anoxic acapnia than in pure acapnia. It could hardly be said from this table that anoxia per se had any significant effect on the CRP.

A similar conclusion is reached from the summary given in table 5 of the experiments of figure 1. The results of the 8 pure acapnia flights and the 7 anoxic acapnia flights are averaged separately. The rise in CRP is  $0.14 \pm .03$  m.v. without anoxia and  $.24 \pm .035$  m.v. with anoxia. The probability that the difference between these two figures is due to chance is 14 out of 100. It can be concluded that in the subjects represented in figure 1 the effect of anoxia is small compared to the effect of acapnia. In C.G.B., however, the effect of anoxia accompanied only by a normal amount of decrease in the  $pCO_2$  gives a

much larger rise in CRP than does a considerably greater acapnia without any anoxia and this suggests that further study might establish a definite small effect due to anoxia in all subjects.

The individual experiments plotted in figure 1 show the general course of the changes which were recorded. Only the 20,000-ft. flights include a curve

TABLE 4. COMPARISON OF THE EFFECTS OF ACAPNIA AND ANOXIC ACAPNIA ON THE CORNEO-RETINAL POTENTIAL (CRP) USING IDENTICAL SUBJECTS

SUBJECT	ACAPNIA WITH O <sub>2</sub>		ANOXIC ACAPNIA	
	Alveolar pCO <sub>2</sub>	Increase in CRP	Alveolar pCO <sub>2</sub>	Increase in CRP
	mm Hg	%	mm. Hg	%
W. O. F. . . . .	12.8	11.6	13.1	12.1
H. R. . . . .	17.0	22.6	16.0	13.3
M. A. E. . . . .	25.0	23.1	20.3	22.4
R. W. S. . . . .	14.4	9.1	20.0	24.2
J. MCW. . . . .	18.6	14.7	18.6	28.2
J. H. . . . .	16.9	8.2	17.5	1.4
M. H. . . . .	15.5	17.3	18.5	28.2
C. G. B. . . . .	18.0	34.4	(25.?)	52.0
Average . . . . .	17.3	17.7	18.6	22.7

TABLE 5. AVERAGES OF CORNEO-RETINAL POTENTIALS (CRP) WITH PROBABLE ERRORS (PE) AT ALTITUDE AND GROUND LEVEL (GL) AS A FUNCTION OF ALVEOLAR pCO<sub>2</sub>

ALTITUDE 10 <sup>3</sup> FEET	AVERAGE pCO <sub>2</sub>	MEAN CRP	PE OF MEAN CRP	MEAN Δ CRP	NO. OF TESTS	NO. OF FLIGHTS
	mm. Hg	m v	m. v	m v		
GL	(40.0)	1.06	.04		43	8
30	35.0	1.09	.12	+0.05	11	4
30	17.2	1.20	.04	+0.14	61	8
GL	(40.0)	1.04	.04	-0.02	43	8
GL	(40.0)	1.10	.04		32	7
20	18.3	1.34	.05	+0.24	58	7
GL	(40.0)	1.12	.03	+0.02	46	7

The percentage incidence of slight, moderate and severe acapnia was 12, 50 and 39 respectively at 30,000 ft. and 15, 71 and 14 respectively at 20,000 ft. Oxygen was inhaled at 30,000 and air at 20,000 ft. All the potentials are given in millivolts. Figures in ( ) are assumed values. Differences in CRP are differences from original GL value. These values for Δ CRP are not always equal to the differences in the mean CRP values because the latter referred to different numbers of flights. Averages obtained from the data of fig. 1.

for arterial saturation. The pCO<sub>2</sub> curves are represented as dropping promptly to a new level when hyperventilation began. This is justified by other experiments in which more frequent analyses of alveolar air were made. The CRP curves show the magnitude of the variations met with and show how the CRP often rises to a peak and then falls even before the pCO<sub>2</sub> begins to rise, as if some process of adaptation had occurred. This suggests that the CRP is not a direct function of pCO<sub>2</sub>, but depends upon a number of factors within the organism

and is, therefore, subject to much variation between individuals. For the statistical study of these data (table 5) representative groups of points were averaged together.

These potentials are not significantly modified by light conditions. In one experiment on *C. G. B.* the values obtained during a preliminary period of light adaptation were reproduced throughout a subsequent 50-minute period of dark adaptation and during 5 minutes of light adaptation thereafter. This is in agreement with previous information for if the eyes are deviated far to one side in the dark and held stationary in that position while a bright light is turned on, the record of the string shows no deflection.

One observation made during the course of these experiments confirms the reports of others, and that is a loss in the precision of ocular movements. McFarland *et al.* (2, 3) have reported such a finding with anoxia—they also found deterioration of eye movements in reading under such conditions. We have found that the movements became generally slower with acapnia, and often the records were very erratic and difficult to measure.

Gross changes in skin (and possibly also retinal) circulation are ineffective in changing normal potentials. One subject, *C.G.B.*, breathing room air received .5 cc. (10 units) pituitrin subcutaneously; marked vaso-constriction (pallor) ensued, but the eye potentials did not vary. During the course of the next half hour, 2 amyl-nitrite inhalations, each sufficient to evoke giddiness, flushing and obvious vaso-dilatation, were ineffective in changing the potentials.

As an explanation of the changes in CRP which have been reported it is natural to think first of the pH change which accompanies acapnia and, to a lesser extent, anoxia. The marked differences between individuals and the failure of the potential to remain constant at a higher level so long as the  $\text{CO}_2$  remains low suggest that other factors must also be involved. On account of this variability, the measurement of the corneo-retinal potential can hardly be recommended as a measure of acapnia.

#### SUMMARY

The corneo-retinal potential is increased about 20 per cent by acapnia with an alveolar  $\text{pCO}_2$  of about 18 mm. Anoxia also increases the potential, but this is largely due to the overventilation and acapnia which accompanies it. In some individuals, however, anoxia itself seems to increase the potentials even more than acapnia.

We are indebted for collaboration in these experiments to Dr. L. E. Chadwick, Dr. M. A. Epstein and Dr. C. G. Bly and to various members of Civilian Public Service Unit No. 115-R who served as subjects for the experiments.

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# *Continuous Analysis of Alveolar Gas Composition During Work, Hyperpnea, Hypercapnia and Anoxia<sup>1</sup>*

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ONE OF OUR OBJECTIVES during the last few years has been to describe the dynamics of the alveolar gas exchange as it is altered by hyperpnea, exercise and changes in the oxygen and carbon dioxide concentrations of the environment. Two factors have greatly contributed to this reanalysis of classical respiratory physiology: *a*) a method for the continuous analysis of alveolar air (1); and *b*) the development of an alveolar air and alveolar ventilation equation (2). The presentation of these respiratory data is greatly facilitated by the use of the  $O_2$ - $CO_2$  diagram (2) which allows the simultaneous visualization of oxygen and carbon dioxide concentrations in the lung, the respiratory quotient, the alveolar ventilation and hemoglobin saturation.

## METHOD

Since our first description of the continuous sampling of alveolar air we have been able to simplify our method so that this device can be easily constructed and installed into any breathing system (fig. 1). A pump delivers continuously 150 ml/min. of alveolar air (the last 10-15 cc. of each tidal volume) to the automatic gas analyzers. Alveolar air is always present in the upper end of the expiratory tube except during the first phase of expiration. To prevent the dead space air from being drawn into the analyzer the alveolar air content of the balloon is pushed back into the main expiratory tube by the positive mask pressure of expiration. This volume far exceeds the pump capacity during this phase. Upon inspiration the balloon is again filled with alveolar air by the negative mask pressure.

## *$O_2$ - $CO_2$ Diagram*

Any alveolar value can be represented by a point when the  $O_2$  is plotted against the simultaneous  $CO_2$  tension. The computed respiratory quotients form straight lines originating at the inspired oxygen tension, while the lines of equal alveolar ventilation lie parallel to each other with a slope of  $-.209$  if air is breathed. Thus the circle in figure 2 represents an alveolar air concentration at sea level. This automatically fixes the R.Q. as 0.85 and the alveolar

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ventilation (if the oxygen consumption is 250 ml/min.) as 4.5 l/min. Any deviation of this point is brought on by alteration in one or more of these factors.

If one goes to high altitude one simply slides the R.Q. and ventilation lines along the abscissa until the origin of the R.Q. lines coincides with the new inspired oxygen tension. Thus in addition the simultaneous  $\text{HbO}_2$  per cent saturation can be read off, if we assume that there is no appreciable gradient between the alveolar air and arterial blood. These iso-saturation lines are determined from the nomogram of Henderson and Dill. The slope represents the Bohr effect.

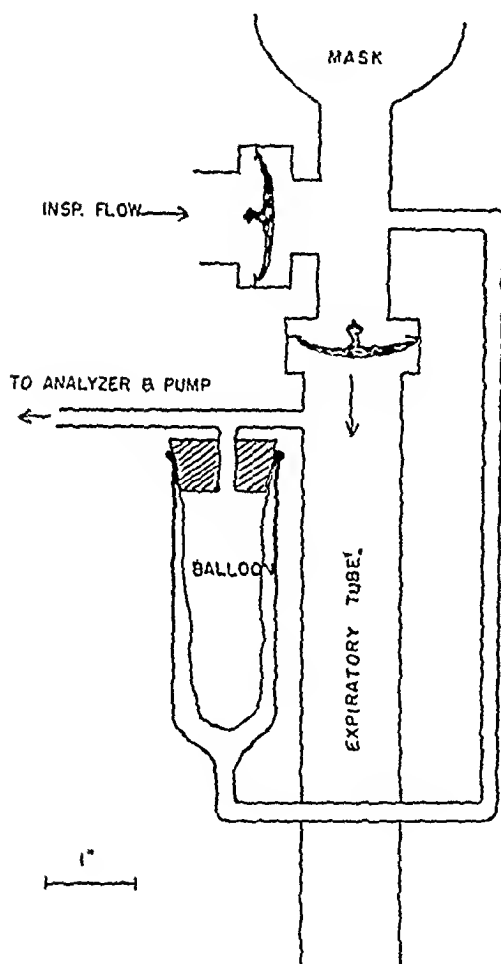


Fig. 1

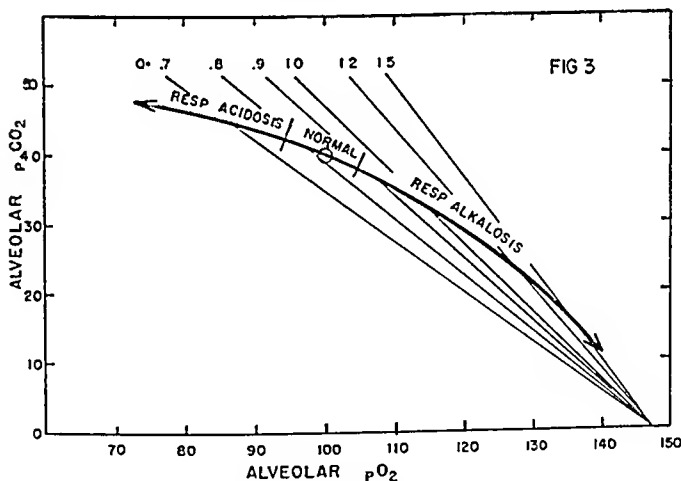
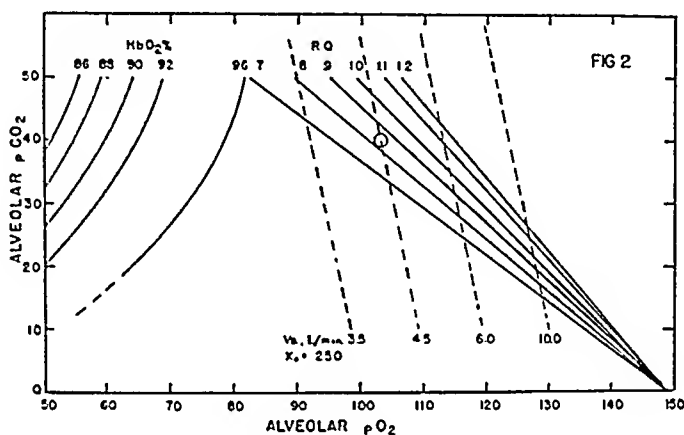
*Primary respiratory acidosis and alkalosis pathway.* The circle in figure 3 represents an average alveolar air concentration. However, repeated determinations show that this point will vary from time to time as indicated by the normal range. This holds true not only in the resting state but also under strict basal conditions in trained subjects as Carpenter and Lee found many years ago (3). If the breath is held for increasing periods this curve can be extended to the left or after a few breaths of hyperventilation to the right as indicated. Thus acute changes in ventilation affect the gas exchange in a very precise manner largely by alterations in  $\text{CO}_2$  output, the oxygen consumption tending to remain constant.

Thus far the initial shift of the normal alveolar air under various conditions (exercise, anoxia, hyperventilation, anesthesia, deadspace increase) has always been observed to follow one of these precise pathways. We might thus refer to these pathways as primary respiratory acidosis and alkalosis pathways which precede the secondary accommodations which will be described below.

It is of interest to speculate here about the so-called unequal gas exchange in the lung. This may be brought about by different ventilation to blood-flow ratios in the various alveoli. A recent theoretical analysis (to be published) supports the concept that the various alveolar gas concentrations that

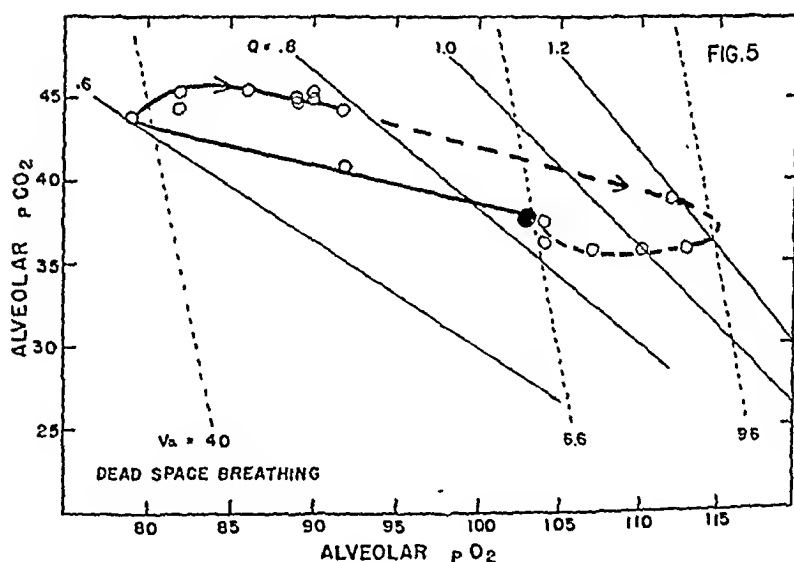
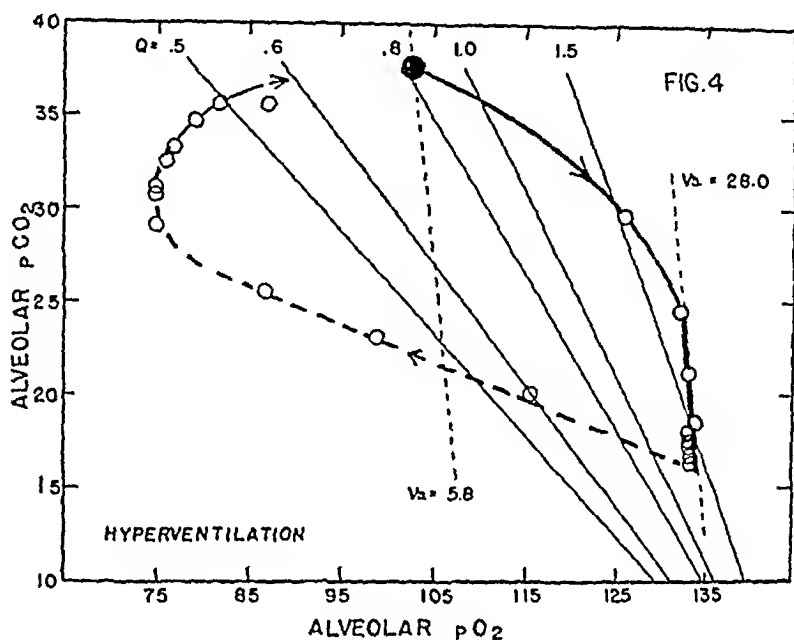
could exist at any one time in the various alveoli are represented by points lying very close to this pathway, and that when combined they give us a mean alveolar air value represented by the circle in figure 3.

*Hyperventilation.* If the alveolar ventilation is suddenly increased and maintained at 28 l/min. the alveolar air composition according to the ventilation equation must at any time lie somewhere along this iso-ventilation line.



The experimental points in figure 4 show the average readings of 4 subjects. Each point represents an interval of 1 minute from the start of hyperventilation where the alveolar  $p\text{CO}_2$  was 37.5 mm. Hg with an R.Q. slightly above 0.8 and an alveolar ventilation of 5.8 liters (solid circle). It can be seen that after the first minute the  $\text{CO}_2$  falls off along the iso-ventilation line for 28 l/min. This fall is rapid at first and cuts across the various R.Q. lines. After 10 minutes a  $p\text{CO}_2$  of 16 mm. was reached with an R.Q. of about 1.3. If ventilation had been maintained beyond this time the steady state would have

been reached at a  $p\text{CO}_2$  of 9 mm. Hg where this particular iso-ventilation line intersects the original R.Q. line of 0.8. The recovery pathway is indicated by the dashed line. The previously incurred alkalosis decreased the ventilation, allowing the  $\text{CO}_2$  stores to be restocked and simultaneously producing a very

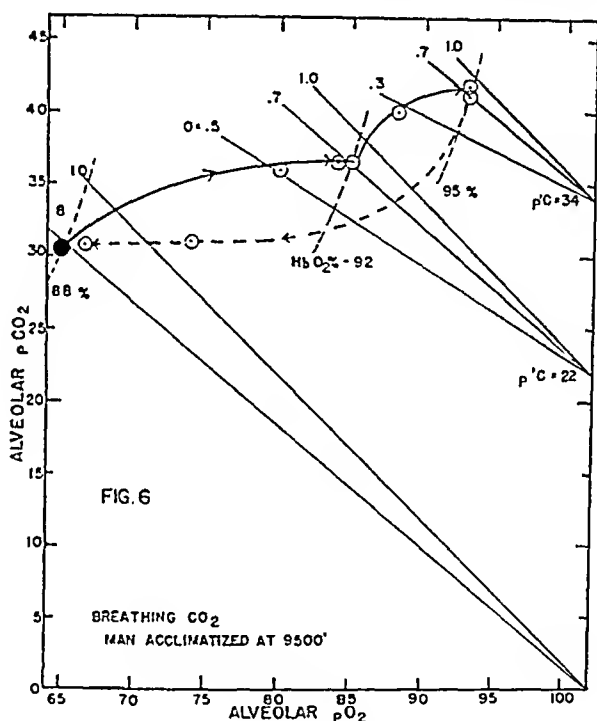


low alveolar oxygen concentration. Even at the end of 10 minutes of recovery the R.Q. is still below 0.6 and recovery is far from complete.

Thus hyperventilation and recovery are represented by a continuous cycle which is bisected by the normal R.Q. line.

*Hypoventilation.* An evenly maintained hypoventilation is difficult to achieve in man but it presents the above picture in reverse. We have attempted this by increasing the dead space by breathing through a tube of

about 1300 cc. With such a device the total ventilation is enormously increased, but the alveolar ventilation decreased. The solid circle in figure 5 shows the normal resting value of 3 subjects prior to breathing on this device for 10 minutes. The hypoventilation pathway is likewise clockwise and each open circle represents successive 1 minute intervals. The alveolar ventilation shows an immediate reduction from 6.6 to 4.0 l/min. and then gradually increases and tends to stabilize with an R.Q. of 0.8 and a  $p\text{CO}_2$  of 45 mm. As may be seen the original R.Q. was not attained during this period, but as can



be predicted from this diagram the alveolar concentrations with further exposures could not have changed very much. Recovery (dashed line) is followed by an immediate rise of alveolar ventilation and high R.Q. indicating that the excess  $\text{CO}_2$  stored is now gotten rid of. After 6 minutes of recovery the original equilibrium has been achieved.

Similar pictures have been obtained during intravenous anesthesia by sodium pentothal in man and in dogs. The depression of the respiratory center and the concomitant fall in alveolar ventilation induce the acidosis shift to the left, while recovery from anesthesia is followed by a compensatory high R.Q. (5).

### Anoxia

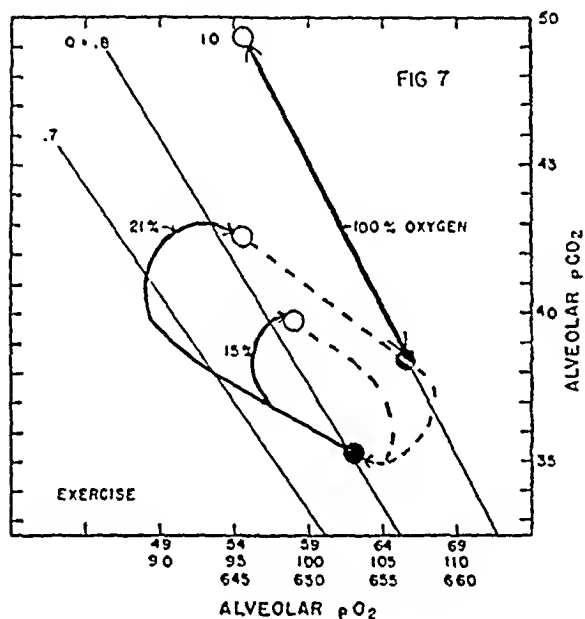
The effects of anoxia have been followed in a large number of individuals in the high altitude chamber (4). The average alveolar pathway for 8 men



exposed for 30 minutes to 22,000' pressure altitude and the ensuing recovery at ground level has been shown in a previously published figure (*Am. J. Physiol.* 150: 214, 1947). It differs from the previous description of voluntary hyperventilation in that the initially maximal ventilation response is not maintained. Thus the pathway returns to its original R.Q. by a horizontal instead of a vertical line and probably represents a compromise between the anoxic stimulus and the concomitant inhibition by respiratory alkalosis. Data collected at various altitudes indicated that the normal R.Q. or the steady state is obtained in 30 to 60 minutes of anoxia.

### *CO<sub>2</sub> in the Inspired Air*

When breathing air the inspired oxygen tension is approximately divided between the alveolar oxygen and the alveolar carbon dioxide, the exact division



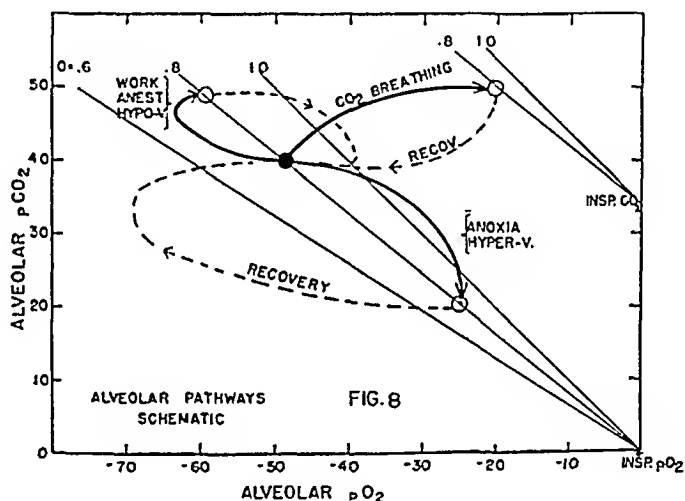
depending upon the R.Q. and the rate of ventilation. The same concept can be applied to the extra CO<sub>2</sub> added to the inspired air. Since the respiratory center responds to slight changes in the arterial CO<sub>2</sub> tension by high ventilatory rates the pCO<sub>2</sub> is prevented from rising very much. Thus when breathing CO<sub>2</sub> with the inspired oxygen tension kept as it was before, the gain in alveolar oxygen can be said to equal roughly the inspired CO<sub>2</sub> tension minus the increase in alveolar CO<sub>2</sub> tension brought about by this maneuver.

This is well illustrated in figure 6 where the change from normal alveolar air (solid circle) is indicated at five-minute intervals when 22 mm. pCO<sub>2</sub> are inspired followed by another 15-minute period breathing 34 mm. pCO<sub>2</sub>. These points represent the average of 3 subjects after three weeks of acclimatization at an altitude of 9500 ft. The inspired O<sub>2</sub> tension was kept identical throughout the experiment. Breathing 22 mm. CO<sub>2</sub> the alveolar CO<sub>2</sub> rose 6 mm. and the alveolar O<sub>2</sub> rose 18 mm. or a total of 24 mm. Hg. With 34 mm. CO<sub>2</sub> in the inspired air the CO<sub>2</sub> and O<sub>2</sub> changed 11 and 26 mm. respectively. Thus at the expense of increased ventilation the alveolar oxygen and oxygen saturation of the hemoglobin (from 88% to 92% and 95%) were greatly increased with relatively little change in alveolar CO<sub>2</sub>. Recovery is shown by the dashed line showing the high R.Q. associated with excess CO<sub>2</sub> excretion. The oxyhemoglobin values were obtained from the ear oximeter.

### Exercise

The fact that the alveolar  $\text{CO}_2$  rises during moderate exercise has been appreciated since the work of Haldane. One might predict that under such circumstances the pathway during exercise would simply proceed up the normal R.Q. line until the new  $\text{CO}_2$  level had been reached. However, this was not the case. The lower solid circle in figure 7 represents the normal resting value of 5 subjects. Upon initiation of exercise (20 cm. step, 20 times/min.) a clockwise swing of the alveolar pathway is observed. This is brought about by a relative hypoventilation with its concomitant fall in R.Q. and alveolar oxygen.

After 3 to 4 minutes a new steady state is reached (open circles) and maintained hereafter with a slightly elevated R.Q. Upon recovery, the R.Q.



rises precipitously as has been observed by others. However, the interpretation that this is largely due to  $\text{CO}_2$  released by lactic acid is not quite tenable. A good share of it must be the metabolic  $\text{CO}_2$  retained during the first part of exercise, which during recovery will be lost in the same way as is the  $\text{CO}_2$  accumulation observed with  $\text{CO}_2$  breathing, dead space breathing or anesthesia where the lactic acid level is not elevated.

Of further interest is the effect of the inspired oxygen tension upon the exercise pathway. Figure 7 shows the pathway breathing 15, 21 and 100 per cent oxygen. While the subjects and exercise were identical in these three experiments the responses differed considerably. The lower the oxygen concentration the greater the ventilation and the smaller the alveolar  $\text{pCO}_2$  and R.Q. change. (With 100% oxygen the R.Q. changes cannot be represented on this diagram and any pathway is limited to the R.Q. = 1.0 line.) This observation suggests that the lower the oxygen tension, the greater

breakdown products which in turn produce a greater stimulation upon the respiratory system. Preliminary exercise tests on patients with lung diffusion troubles were studied in collaboration with the Department of Medicine. These patients give a response very similar to normal man under low oxygen tension. In fact, in some advanced cases there is practically no change in the alveolar air during exercise.

Thus these work loops might give a quantitative assay of the respiratory efficiency during exercise. The larger the loops, the more efficient the performer.

#### SUMMARY

The  $O_2$ - $CO_2$  diagram offers a new approach to the quantitative description of various respiratory phenomena, since it allows the simultaneous visualization of alveolar oxygen, carbon dioxide, respiratory quotient and ventilation. This approach is made particularly useful with the continuous recording of alveolar gas composition. Experiments have been performed which indicate that the alveolar gas concentration can be varied in certain directions only, and along certain pathways. This in a large measure is controlled by the changes in  $CO_2$  output which varied with the relative ventilation. Figure 8 summarizes the principal pathways that have been observed during hyperpnea, anoxia, hypoventilation, exercise and  $CO_2$  breathing as well as the pathways of recovery.

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# Daily Variations of Vital Capacity, Residual Air, and Expiratory Reserve Including a Study of the Residual Air Method<sup>1</sup>

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THE PURPOSE OF THESE EXPERIMENTS was to determine the daily variation to be expected in the measurement of the vital capacity and the residual air in a single individual from day to day. No such data were found in the literature with the exception of those given for vital capacity by Griffith *et al.* (1) on 6 subjects extending over a period of a year or more. The data agreed with ours in showing the same standard deviation of the vital capacity and an absence of seasonal variation.

**Vital Capacity.** Daily values, except on Sundays, were obtained on 12 men and 5 women over a period of 2 to 3 months from September to December. Subjects were always seated and the determinations were made between 4 and 5 o'clock in the afternoon. The highest value of 3 trials was recorded as vital capacity. The spirometer temperature and the barometric pressure were recorded and the volumes were expressed at body temperature, pressure, saturated (B.T.P.S.).

The average results are recorded in table 1. The average vital capacities of all the individuals examined range from 3231 to 6293 cc. with standard deviations ranging from 59 to 193 cc. The average of all the standard deviations is 111 cc. which is 2.36 per cent of the average vital capacity of 4720 cc.

In 5 male subjects the vital capacity was also determined in the morning between 9 and 10 o'clock on about 35 different days, over a period of about 2 months. A comparison of these values with the afternoon values indicates no significant difference in either volume or standard deviation (table 2).

**Residual Air.** These measurements were carried out 5 times a week for 7 weeks on 5 male subjects by a modification of the method of Lundsgaard and Van Slyke (2). The details of this procedure are discussed below. These values were obtained between 9 and 11 o'clock in the morning with the subject

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in a seated position. At the same time the vital capacity and expiratory reserve<sup>2</sup> were measured. The averages of the figures obtained in these measurements are given in table 3 together with the standard deviations. The coefficient of variation of the residual air measurement is nearly three times that for the vital capacity on the same people. The average residual air volume in the sitting position is 30 per cent of the vital capacity and 23 per cent of the total capacity.

TABLE 1. MEAN VITAL CAPACITIES IN 17 SUBJECTS

SUBJECT	DAYS	VITAL CAP.	S. D.	SUBJECT	DAYS	VITAL CAP.	S. D.
		cc.	cc.			cc.	cc.
1.....	18	5684	142	10.....	73	5231	95
2.....	71	6293	141	11.....	62	4677	193
3.....	80	4083	92	12.....	72	4762	100
4.....	74	4978	59	13.....	42	3371	74
5.....	81	4768	71	14.....	52	4332	85
6.....	82	5557	154	15.....	62	3597	178
7.....	74	4782	90	16.....	64	3648	66
8.....	46	5124	88	17.....	58	3957	145
9.....	74	5408	90	Average.....		4720	111

All subjects were males except numbers 13-17.

TABLE 2. VITAL CAPACITIES IN A.M. AND P.M. COMPARED

SUBJECT	N	V. CAP. A. M.	S. D.	V. CAP. P. M.	S. D.
		cc.	cc.	cc.	cc.
R. S.....	34	4800	72	4770	69
H. R.....	35	6260	138	8300	140
H. M.....	38	4980	75	4980	89
W. L.....	36	5270	121	5250	73
J. H.....	35	4110	70	4050	91
Average.....		5084	95	5070	92

All values in cc., B.T.P.S. N = no. of days on which observations were made.

*Effect of Environment.* These studies were begun in August and carried on to the end of November 1945. No subjects exhibited any seasonal change during this relatively brief period but simply varied around the mean. The room temperature, humidity and effective temperature as well as barometric pressure were recorded every day. None of these factors showed any correlation with the lung volume fluctuation except the dry bulb temperature. In 5 individuals the vital capacity increased on the average 170 ml. between

<sup>2</sup> Expiratory reserve includes all the air which can be expelled by forcible expiration beginning at the end of a normal expiration.

20° and 30°C. One subject was excluded from this series due to his periodic attacks of asthma resulting in large fluctuations of his vital capacity. It is of interest to note that these fluctuations occurred without change in his total capacity. This is shown by the grouping of points around the negative slope of 1.0 when his vital capacity is plotted against his residual air volume (fig. 1).

*Residual Air Method.* A modification of the Lundsgaard-Van Slyke (2) method for the determination of residual air was evolved after a long series of preliminary studies on the same subjects eventually used for the daily test. The subject breathed air through a metal three-way stopcock which had a dead space of 40 cc. This value was later subtracted from the residual air volume. After a complete, forced expiration, the subject was connected by a turn of the stopcock to a spirometer containing 2040 cc. of 100 per cent oxygen.

TABLE 3. REPEATED DETERMINATIONS OF RESIDUAL AIR, EXPIRATORY RESERVE AND VITAL CAPACITIES OF 5 SUBJECTS

SUBJECT	DAYS	RESIDUAL AIR		EXP. RESERVE		VITAL CAP.		TOTAL CAP.	
		Mean	S. D.	Mean	S. D.	Mean	S. D.	Mean	S. D.
R. S.....	35	1380	57	2125	109	4800	72	6165	93
H. R.....	36	2126	94	2517	169	6258	138	8371	187
H. M.....	37	1440	78	1242	134	4976	75	8415	128
W. L.....	37	1657	101	2087	142	5270	121	6920	138
T. H.....	37	1077	90	903	146	5100	70	5188	125
Average.....		1536	84	1775	140	5084	93	6612	130

All volumes and standard deviations in cc., B.T.P.S.

The dead space of the spirometer plus the tube connecting the spirometer and the stopcock were also filled with O<sub>2</sub> and had a volume of 460 cc. The subject then inhaled and exhaled the full contents of the spirometer (2040 cc.) once every 3 seconds by watching a clock. At the end of the third expiration an alveolar sample was drawn for analysis and the volume of the residual air was calculated from the percentage of nitrogen which was found. Duplicate gas analyses were made with a Fry analyzer, and any readings that differed by more than 0.2 per cent were discarded. No greater accuracy is required for lung volume determination.

The calculations of the residual air are made as follows:

Let  $f_N$  and  $f'_N$  = fractions of N<sub>2</sub> in the alveolar air before and after mixing respectively;  $V_R$  = volume of the residual air in ml. B.T.P.S.;  $V_S$  = volume of the spirometer and dead space (2,500 ml.) in ml. at room temperature and pressure, saturated;  $B$  = atmospheric pressure at time of the test;  $t$  = temperature in the spirometer;  $p_{H_2O}$  = vapor pressure in the spirometer, 40 = dead space in stopcock in ml.

$$\text{Then } V_R = V_S \frac{f'_N}{f_N - f'_N} \times \frac{B - p_{H_2O}}{B - 47} \times \frac{310}{273 + t} - 40 \quad (1)$$

The modification of the method consists in 1) assuming 80 per cent instead of 79.1 per cent for the nitrogen content of the normal alveolar air prior to the inhalation of  $O_2$ ; and 2) in analyzing the mixture after the third rebreathing rather than the fourth or fifth as originally advocated. The reasons for these changes are explained below.

Hundreds of determinations in this laboratory have shown that the average alveolar R.Q. when determined by a forced expiration at the end of a normal expiration during rest in the sitting position is 0.80. With an alveolar  $pCO_2$  of 40 mm. this would mean that the nitrogen percentage is about 80.0 just prior to mixing with the pure oxygen. A value of 79.1 per cent can be obtained only if the alveolar R.Q. is unity. An error of 1 per cent in this value for  $fN$  is equivalent approximately to an error of 40 cc. in the final residual air volume.

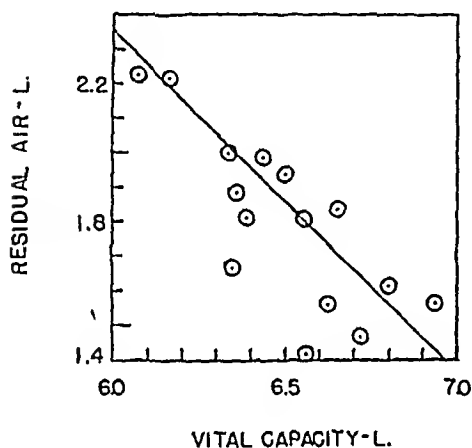


Fig. 1. Exceptional data on one subject, M.E., who was subject to asthmatic attacks. When his vital capacity decreased his residual air volume increased an equal amount.

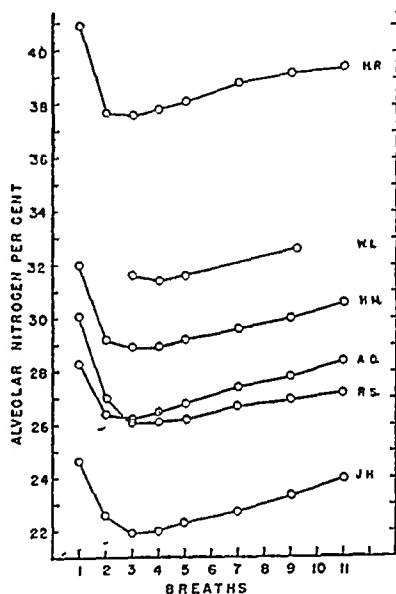
The formula (equation 1) for the calculation of the residual air is based upon the assumption that the amount of nitrogen in the lung-spirometer system does not change during the mixing. On account of the suddenly lowered nitrogen tension in the lung, from 80 per cent to 30 per cent, this is not strictly true, but the error is smaller than the error of the nitrogen analysis. The amount of nitrogen which could enter the lungs under these conditions can be calculated by assuming a cardiac output of 5 l/min. and a lung-blood nitrogen gradient of about 350 mm. Hg (i.e.  $(80\% - 30\%) \times 700$ ) and an absorption coefficient of nitrogen in blood of 0.011. Thus, in 10 seconds (3 breaths)  $\frac{5000}{6}$  cc.  $\times$  0.011 or 4.2 cc. of nitrogen would come into the lungs under the most favorable conditions. This represents about 0.1 per cent increase of nitrogen in a lung-spirometer volume of 4000 cc. We have made no correction for this small error.

While this correction for diffused nitrogen can safely be neglected, the change in volume due to the consumption of oxygen and the output of  $CO_2$  is

more important. Immediately after mixing the alveolar and spirometer air, the  $p\text{CO}_2$  is reduced to less than half the normal value so that  $\text{CO}_2$  pours into the lung rapidly from the blood. Thus, the R.Q. must be well above unity in the first few seconds after mixing starts but rapidly diminishes to abnormally low values owing to the large storage capacity of the body. It will be shown, however, that for the period of the first 3 breaths the average R.Q. is nearly 1.0 so that at this particular point the volume change is negligible.

The quantitative aspects of this problem were investigated by analysing alveolar samples (5 cc. each) from successive breaths for nitrogen. The figures

Fig. 2. Alveolar nitrogen percentages during mixing with inhaled oxygen in 6 subjects. Each curve is the average of three separate experiments.



obtained on 6 different subjects for nitrogen are plotted in figure 2. Each point represents the average of 3 separate trials. In every case the nitrogen percentage drops from a normal value of 80 per cent to 20 or 30 per cent as a result of the inhalation of oxygen. A minimum value is reached at about the third breath when the mixing may be regarded as practically complete. After this the nitrogen percentage slowly increases. This slow increase is too great to be accounted for by the elimination of nitrogen from the blood but is due rather to the decrease in volume of the lung-spirometer system due to the absorption of oxygen with a very small  $\text{CO}_2$  output.<sup>3</sup> It is tempting to extrapolate this slowly rising curve to zero time and to take the extrapolated nitrogen percentage for the calculation of the residual air. This would presumably be correct if the R.Q. remained constant during the rebreathing but this is not the case. During the early stages of the rebreathing the  $\text{CO}_2$  tension is much

<sup>3</sup> A similar low R.Q. is found during breath holding which we have discussed elsewhere (13).



below normal and  $\text{CO}_2$  must be coming off into the lungs at a very high rate. The volume of the lung-spirometer system must therefore be actually increasing rather than decreasing during the first few breaths. To calculate the residual air, therefore, it is necessary to find the nitrogen percentage for a theoretical instantaneous mixing of the lung and spirometer air or, in other words, the nitrogen percentage which prevails at a time when the volume of the system is the same as it was at the beginning of the rebreathing. When the volume is the same the average R.Q. from the beginning will necessarily be equal to 1.0.

It might at first be supposed that the minimum of the nitrogen curves in figure 2 represents the time when the R.Q. is changing from values above 1 to values below 1. This is not necessarily the case however because the initial fall in the nitrogen percentage is largely due to the progress of the mixing process which overshadows the volume changes.

The theoretical speed of attainment of homogeneity can be calculated from the volume of the residual air, the dead space connecting the lungs with the stopcock and the spirometer and the volume of the spirometer which was assumed to be emptied at each breath. It is assumed that there is no gas exchange in the lungs and complete mixing in the alveoli. With 80 per cent nitrogen in the lungs to begin with and 0 per cent in the spirometer (pure oxygen) the values for the nitrogen percentage in the spirometer and the lungs respectively after the first three expirations were calculated as shown in table 4.

This calculation partially justifies the use of the third expiration for the calculation of the theoretical percentages for instantaneous mixing from equation 8 and confirms some similar calculations from rebreathing experiments on models by Rauwerda (3).

In order to investigate the changes in the R.Q. during different phases of the rebreathing period we have studied two subjects in greater detail, analyzing consecutive breaths for  $\text{CO}_2$  and  $\text{O}_2$  as well as nitrogen. The figures are given in table 5 and are plotted in figure 3. The oxygen percentage increases rapidly until about the third breath and then diminishes at a more or less linear rate as determined by the rate of oxygen consumption of the body and the volume of the gas. Conversely the  $\text{CO}_2$  percentage diminishes rapidly at the first breath and then increases at first very rapidly and then more slowly. The striking fact is that the  $\text{CO}_2$  does not diminish as much as would be expected from the dilution of the nitrogen. This is shown by the two lowest curves in figure 3 calculated by the expression  $\frac{5.3 \text{ fN}}{80}$  where 5.3 is the assumed

initial alveolar  $\text{CO}_2$  percentage and fN is the fraction of nitrogen found in the alveolar sample taken at the breath in question. This calculated curve represents the concentration of  $\text{CO}_2$  which would have obtained had there been no  $\text{CO}_2$  output whatever during the experimental period and the interval be-

tween this curve and the observed curve represents, therefore, the actual rate of CO<sub>2</sub> output; this rate is high at first but soon approaches a plateau. These rates are slightly exaggerated during the first two breaths because at that time the mixing is not quite complete between the alveoli and the spirometer and the CO<sub>2</sub> percentage is slightly higher in the lung fraction. The dotted lines

TABLE 4. COMPLETENESS OF MIXING AFTER THE THIRD BREATH

EXPIRATIONS	SPIROMETER	NITROGEN PERCENTAGE	LUNGS
0	80.0		0
1	26.6		34.4
2	31.9		33.4
3	33.2		33.3

TABLE 5. CHANGES IN THE COMPOSITION OF THE ALVEOLAR AIR IN TWO SUBJECTS DURING REBREATHING

NO. OF BREATHS	SUBJECT 1						SUBJECT 2					
	O <sub>2</sub>			CO <sub>2</sub>			O			CO <sub>2</sub>		
	per cent			cc/m <sup>2</sup> n.			per cent			cc/min.		
0.....	68.38	1.92	29.65				59.11	2.54	38.35			
1.....	63.73	3.9	32.4		1300		52.27	4.23	43.5			1180
2.....	65.59	4.41	30.0		699		56.61	4.79	39.1			1093
3.....	65.64	4.86	29.5	644	431		56.36	5.54	38.3	898		865
4.....	65.30	5.25	29.4		317		55.45	5.85	38.7			249
5.....	64.75	5.65	29.6	423	309		54.90	6.00	39.1	1280		85
7.....	63.73	6.17	30.1	874	171		53.90	6.40	39.7	895		149
9.....	63.04	6.61	30.4	542	150		53.09	6.72	40.2	721		119
11.....	62.30	6.80	30.9	708	33							

Volumes of lung spirometer system for calculation of rate of gas exchange were 4065 and 4970 cc. respectively for subjects 1 and 2. Corresponding residual air volumes were 1565 and 2470 cc. The expiratory reserve and total dead space were taken as 2000 and 500 cc. for both subjects. Each figure for O<sub>2</sub> intake or CO<sub>2</sub> output refers to the preceding interval. A blank indicates that the rate for this interval was included in the figure for the next interval. Thus in subject No. 2 the CO<sub>2</sub> output for the 0-1 interval was 1180 cc/min. and the O<sub>2</sub> intake for the 0-3 interval was 898 cc/min. Each breath lasted 3 seconds. The rates of O<sub>2</sub> and CO<sub>2</sub> exchange were calculated from the expression  $\frac{V}{t} \left( f'O - f''O \frac{f'N}{f''N} \right)$  where  $f'$  and  $f''$  refer to the breaths before and after the time interval,  $t$ . The rates were so calculated according to equation 8 as to make the rates of oxygen consumption identical in intervals 0 to 3 and 3 to 7.

are extrapolations for oxygen and CO<sub>2</sub> to the points of theoretical instantaneous mixing. The method of calculating these points will be given below.

As was stated previously the extrapolated nitrogen percentage in figure 2 is too low for the calculation of the residual air and it is necessary to obtain the nitrogen percentage at the time of instantaneous mixing. One method of doing this was used by Rauwerda (3). He made measurements of the initial and final volume of the system by terminating as well as beginning

the experiment with a maximal expiration. From the change in this expired volume and a rough estimate of the total volume of the system he was able to correct his final nitrogen value obtained after the twentieth breath to find the correct value at the initiation of the mixing period. We have chosen a different method based upon the assumption that the oxygen consumption

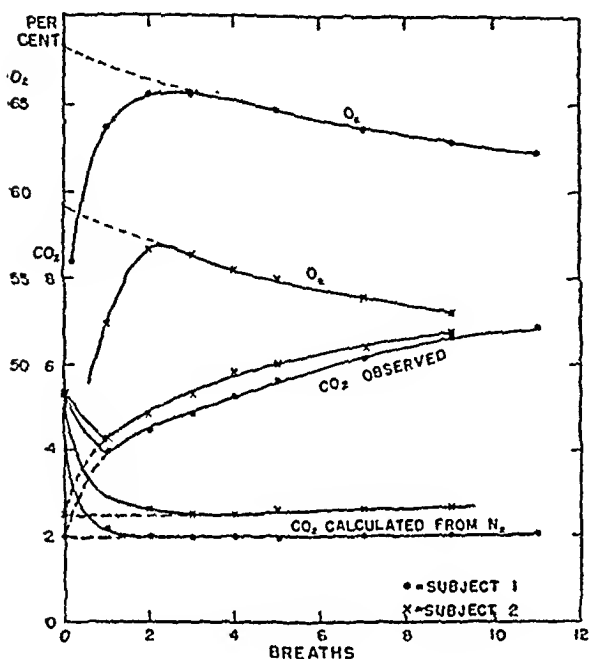


Fig. 3. Changes in the alveolar gas composition of two subjects while rebreathing in the determination of the residual air volume.

remains constant during the period of rebreathing. The method of calculating this is given below.

Let  $f$  = the fraction of a gas in the alveoli before mixing;  $f'$  = the fraction calculated after an instantaneous mixing with spirometer air;  $f''$  = the fraction after the third breath;  $f'''$  = the fraction after a later breath;  $t_1$  = the time in minutes between the  $f'$  and  $f''$  sample;  $t_2$  = the time in minutes between the  $f''$  and  $f'''$  sample;  $V, V', V'',$  and  $V'''$  = the volumes (in ml. B.T.P.S.) of the lung-spirometer system at times corresponding to  $f, f', f'',$  and  $f'''$  ( $V$  = residual air only);  $X$  = cc. of  $O_2$  (B.T.P.S.) lost from lung per minute;  $N, C,$  and  $O$  = nitrogen, carbon dioxide and oxygen respectively. Assuming that  $X$  is the same during the two time intervals,  $t_1$  and  $t_2$ ,

$$X = \frac{f'OV' - f''OV''}{t_1} = \frac{f''OV'' - f'''OV'''}{t_2} \quad (2)$$

Assuming that the nitrogen in the lung-spirometer system is constant

$$fNV = f'NV' = f''NV'' = f'''NV''' \quad (3)$$

Substituting in (2) values of  $V', V'',$  and  $V'''$  from (3)

$$\frac{f'O \frac{fNV}{f'N} - f''O \frac{fNV}{f''N}}{t_1} = \frac{f''O \frac{fNV}{f''N} - f'''O \frac{fNV}{f'''N}}{t_2} = X \quad (4)$$

$$\text{or} \quad f'O = f'N \left( \frac{t_1 + t_2 f''O}{t_2 f''N} - \frac{t_1 f'''O}{t_2 f'''N} \right) \quad (5)$$

$$\text{But} \quad f'O + f'C + f'N = 1.0 \quad \text{And} \quad f'C = \frac{fCI'N}{fN} \quad (6)$$

$$\text{Then} \quad f'O = 1 - f'N - \frac{fCI'N}{fN} \quad (7)$$

Equating (7) and (5) and rearranging

$$1 = f'N \left( 1 + \frac{fC}{fN} + \frac{t_1 + t_2 f''O}{t_2 f''N} - \frac{t_1 f'''O}{t_2 f'''N} \right) \quad (8)$$

In table 5 are given all the values of  $fO$ ,  $fC$  and  $fN$  at different breaths for two subjects as was previously mentioned. The values at breath No. 0 are for instantaneous mixing (i.e.,  $f'O$ ,  $f'C$  and  $f'N$  calculated as described from equations 6, 7, and 8). The rates of oxygen consumption and  $CO_2$  output were calculated from a modification of equation 4 for various intervals assuming the lung volumes given under table 5 (see legend).

The most important feature of table 5 is the value of  $f'N$  which agrees remarkably closely with the value of  $f''N$  or the  $N_2$  percentage after the third breath. Thus as a result of two opposing errors, the third breath value, in these two subjects at least, is almost exactly equal to the theoretical instantaneous dilution value which is needed for the calculation of the residual air. In other words, at the time of the third breath, the decrease in volume resulting from the consumption of  $O_2$  is just equal to the increase from the gain in  $CO_2$ . The ideal point for sampling is then the point where the R.Q. for the period from the moment of mixing is equal to 1.0.

Inspection of the calculated rates of  $O_2$  consumption and  $CO_2$  output in table 5 shows 1) that the rate of  $O_2$  intake is higher than normal but remains apparently constant throughout the experiment; and 2) that the rate of  $CO_2$  output is much higher than the  $O_2$  intake rate at first (R.Q. = 1.0) and falls to very low values (R.Q. = 0.2) at the end.

The values of  $f'N$  and  $f'O$  (table 5 breath No. 0) were so calculated as to make the rate of  $O_2$  intake during the first 3 breaths equal to the rate in the next 4 breaths when both are corrected to the same initial lung volume or  $N_2$  percentage by equation 4.

The rates of oxygen consumption given in the table however are calculated for each interval separately without this common correction (see legend, table 5). While the figures therefore are not strictly comparable because the nitrogen percentage does change slightly, this correction is nevertheless smaller than the error of timing the breaths and the general constancy of the values is significant and helps to justify the assumption of a constant rate of oxygen consumption during the procedure upon which equation 8 was based.

The absolute values of these rates of oxygen consumption are also independent of any assumptions made in the calculations and the values found (638 and 965 cc/min.) are over twice the expected normal value of 300 cc. According to Armitage and Arnott (4) the rate of oxygen consumption is increased from 350 to 700 cc/min. by a single deep inspiration due to a suddenly increased circulation through the lungs. Data were not presented to support this conclusion but it might be doubted whether the result is not due to unequal ventilation of different parts of the lungs. When a deep breath is taken some of the air from underventilated alveoli with a low oxygen content might be brought into the mixture and would then simulate an increased oxygen consumption. This may also explain the excessively rapid fall in the concentration of oxygen which occurs during a single deep expiration, an observation which led Krogh and Lindhard (5) to postulate likewise a sudden increase in the rate of oxygen consumption during a single deep breath.

If however the high observed rate of  $O_2$  consumption were due to incomplete mixture in the lungs it would appear only in the first breath and would not continue throughout the period of observation. In our experiments therefore it seems more probable that the cardiac output is increased for the duration of the rebreathing period, which is approximately one circulation time. Christie (6) has brought forward similar evidence of a 90 per cent increase in cardiac output during 20 sec. of hyperventilation and Rauwerda (3) has confirmed this by observations on the rate of uptake of acetylene during rapid rebreathing. After recirculation begins, the rate of oxygen consumption would presumably return to its normal level.

The high initial rate of carbon dioxide output of around 1200 cc/min. (table 5) calls for some discussion. In the first place the average R.Q. during the first three breaths must be nearly 1.0 because the nitrogen percentage at this point is equal to the calculated nitrogen percentage for instantaneous mixing ( $f'N$ ). Immediately after the third breath at least the rate of  $CO_2$  output is definitely less than the rate of oxygen intake. It seems likely therefore that the R.Q. is above 1.0 at the first breath and below 1.0 at the third breath. The reliability of the figures for  $CO_2$  output given in table 5 for the first three breaths is open to some question because the mixing with dead space oxygen was certainly not complete at this time. This incomplete mixing makes any calculations of oxygen consumption totally unreliable during this period and indeed while the oxygen percentage is increasing the calculated rate of oxygen consumption would be negative. The error due to this incomplete mixing would however be some 15 times greater for  $O_2$  than for  $CO_2$ . We would discount therefore the exact figures for  $CO_2$  output during this period but nevertheless believe that the initial R.Q. must be greater than 1.0. Since we do not have reliable figures for discussion it is hardly worthwhile to try to account quantitatively for the high figures of some 1200 cc/min. which

are given. It will suffice to mention that such high rates could not be obtained at the observed alveolar  $\text{CO}_2$  tensions without assuming that the cardiac output was increased. This lends further support therefore to the hypothesis advanced to explain the high rates of oxygen consumption.

In conclusion, the residual air should be calculated, if possible, from the nitrogen percentage which results from instantaneous mixing. This can be calculated by *equation 8* if the alveolar air from successive breaths is obtained, on the assumption that the rate of  $\text{O}_2$  consumption remains constant. In practice, however, it is shown that the nitrogen percentage after the third breath approximates the instantaneous mixing value so that a single sampling after the third breath can be used conveniently to obtain a correct value.

The recommended procedure for the determination of the residual air is therefore as follows: First expire maximally and turn the cock to the spirometer. Inhale pure oxygen from the spirometer emptying it completely, then exhale the same volume. Repeat this three times at 3-second intervals. The third breath is ended by a maximal expiration and the taking of an alveolar sample which is analyzed for nitrogen. This value of  $f'\text{N}$  is used in *equation 1* for the calculation of the residual air.

This method for residual air is useful for cooperative subjects but could not serve well for patients. For such cases the more prolonged normal re-breathing periods recommended by Cournand *et al.* (7) or an open circuit method of Darling *et al.* (8) or Bateman (9) is preferable. We have made no attempt to validate this method against other methods such as those already mentioned and those of Van Slyke and Binger (10), Hurtado *et al.* (14), Rohland (11) and Birath (12). Nor would we claim any superiority for this method over certain others. It is a convenient method in our hands and some of the details of the gas exchange which occurs during the re-breathing period seem to us of general interest for respiratory problems.

#### SUMMARY

Daily measurements were made of the vital capacities of 17 individuals over a 2- to 3-month period. The average of the standard deviations was 2.36 per cent of their vital capacity volume. Daily measurements of the residual air by a nitrogen dilution method on 5 subjects over a period of two months gave an average standard deviation of 5.5 per cent of the residual air volume. The expiratory reserve and the vital capacities of these same individuals had an average standard deviation of 7.9 per cent and 1.9 per cent respectively for their particular volumes.

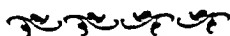
Reasons for the modification of the Lundsgaard-Van Slyke method for the determination of residual air are discussed. A method of calculating the nitrogen percentage for instantaneous mixing is given and it is shown that this is approximately equal to the nitrogen percentage after the third expira-

tion. The latter value is therefore used in practice for the calculation of the residual air.

We are indebted to Mr. Hobart Mitchel, a member of Civilian Public Service Unit No. 115-R, for his meticulous care in carrying out the gas analyses required in this work.

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# Effect on Marksmanship of Some Motion Sickness Preparations Containing Barbiturates and Hyoscine<sup>1</sup>

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IT IS NOW WELL ESTABLISHED by the studies of Holling, McArdle and Trotter (1), Tyler (2) and others (3-5) that hyoscine, either alone or in combination with barbiturates or other belladonna alkaloids, is very effective in preventing sea- and airsickness. Other reports indicate that some of these preparations can be given with safety to enlisted personnel for it appears that little or no significant alterations are produced in physiological, biochemical or psychomotor functions by the dosages ordinarily employed (6, 7) even under conditions of excessive fatigue and stress (8). There is nevertheless considerable reluctance to administer such preparations to individuals whose duties require a high degree of skill, which is understandable in view of the nature of the drugs.

This report deals with the effects of some motion-sickness preventives on the marksmanship of both highly skilled as well as unselected military personnel. The results indicate that one such preparation, rather than having any adverse effects, significantly improved the marksmanship of *unselected* military personnel.

## METHODS

Three types of motion sickness preventives<sup>3</sup> were used in this study: 1) 'MSP' (Motion Sickness Preventive, Army Development Type), a capsule containing amytal, 65 mg. hyoscine, 0.2 mg. and atropine, 0.15 mg. 2) 'RCN', a capsule of niacin, 100 mg. hyoscine, 0.15 mg. and hyoscyamine, 0.4 mg. 3) 'V-12', a capsule of ethyl-beta methylallyl thiobarbituric acid, 130 mg. In all experiments the dosage was two capsules. The placebos used were lactose in capsules identical in color and size to the above capsules.

Two studies, involving a total of 283 men, were made. In the first, 186 marines, comprising an entire company, served as subjects. They had just completed a four-week training period on the marine combat rifle course and were ready for final testing for qualification in one of the various classes of rifle men (Marksman, Sharpshooter or Expert). The usual routine at this stage was to have the men fire a 'preliminary fire,' then two days later "fire for the record." For the preliminary or control fire all men were given placebos.

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<sup>3</sup> MSP and placebos were supplied by Eli Lilly & Company, V-12 and placebos by the Abbott Laboratories. We wish to express our appreciation of the generous aid given by these firms.



They were allotted 68 rounds for a possible score of 340 and fired the regulation marine combat rifle course. All men used the M-1 Rifle and fired from each of four positions: standing, sitting, kneeling and prone, at ranges of 200, 300 and 500 yards. Scores were recorded by instructors at two points, on the range and in the pits. In cases of differences, the pit scores were accepted as final. Two days later, for the record or test fire, the men were divided at random into three groups: one group of 63 men again received placebos; a second group of 61 men received RCN capsules and a third group of 62 men received MSP capsules. As in the control fire, the capsules were taken at 0500. Firing started at 0700 and was completed by 1200. Light, temperature and weather conditions on the test day were the same as on the control day.

The second study was made on 97 instructors at the marine rifle range. These men were experienced riflemen who had qualified as 'Expert' some time previous to this test. At 0650 all men took placebo capsules and at 0745 they fired a control fire. Each man was allowed 5 'sighters' and then fired 16 rounds in an allotted time of 1 minute 5 seconds. All started firing on command and the targets were immediately lowered after the elapsed time. The range was 200 yards. At 0800 one group of 46 men (selected at random) were again given placebos and another group of 51 men were given 260 mg. of 'V-12'. At 0930 the men again fired exactly as in the first fire. At 1100, and without any further medication, they fired again under similar conditions except that the range was increased to 300 yards.

TABLE 1. PERCENTAGE QUALIFYING ON CONTROL AND TEST FIRE

	1 PER CENT QUALIFIED ON CONTROL FIRE <sup>1</sup>	2 ESTIMATED QUALIFICATION FOR TEST FIRE	3 PER CENT QUALIFIED ON TEST	DIFFERENCE BETWEEN COLUMNS 2 & 3
Placebo.....	76.2	83.0	82.5	-0.5
RCN.....	85.5	93.0	90.0	-3.0
MSP.....	79.1	86.0	88.9	+3.8

<sup>1</sup> All men received placebos for the control fire.

In both experiments, neither the subjects nor the scorekeepers were aware of the nature of the medication given.

## RESULTS

In the first study, in order to qualify a man had to score 268 or better. A score of 268 to 291 qualified him for the class of 'Marksman'; 292 to 305, 'Sharpshooter'; and 306 or better, 'Expert.' Those who scored less than 268 were classed as 'Unqualified.'

The percentage that qualified on both the control and test fire are given in table 1. It can be seen that regardless of the medication there is an increase in the number qualifying on the second or test fire. Drawing on the experience of thousands of qualification trials, training officers in charge of a rifle range are able to predict with reasonable accuracy the number that will qualify on a record fire by the percentage qualifying on the preliminary fire. Table 1 shows that the administration of the motion sickness remedy did not significantly affect the percentage expected to qualify. It is to be noted that among

the group receiving MSP the percentage qualifying is slightly higher than predicted, while among the placebo and RCN groups the percentage is slightly lower.

The distribution of the men into the various classes as a result of both fires is shown in table 2. Among the group that received placebos on the test fire 8 more qualified as Marksman, 4 being drawn from those who failed to qualify on the first fire and 4 dropping from the Sharpshooter class. On the other hand, the groups taking the remedies showed a shift to the higher cate-

TABLE 2. DISTRIBUTION OF THE MEN IN THE VARIOUS CLASSES

	CONTROL FIRE	TEST FIRE	CHANGE
<i>Qualifying as Expert</i>			
Placebo.....	1	1	0
RCN.....	7	6	-1
MSP.....	3	8	+5
<i>Qualifying as Sharpshooter</i>			
Placebo.....	19	15	-4
RCN.....	16	24	+8
MSP.....	18	25	+7
<i>Qualifying as Marksman</i>			
Placebo.....	28	36	+8
RCN.....	29	25	-4
MSP.....	28	22	-6
<i>Not Qualifying</i>			
Placebo.....	15	11	-4
RCN.....	9	6	-3
MSP.....	13	7	-6

TABLE 2A. SHARPSHOOTER-EXPERT CLASSES COMBINED

	CONTROL FIRE	TEST FIRE	CHANGE
Placebo.....	20	16	-4
RCN.....	23	30	+7
MSP.....	21	33	+12

gories. This becomes more evident if we combine the Sharpshooter and Expert classes into one category (table 2A); in this case, we find that on the test fire the placebo group dropped 4, the RCN gained 7 and the MSP gained 12.

Table 3 shows the changes that occur in the average scores of each medication group as a whole. The mean scores found on the control fire show that the 3 groups were about equal. On the test day the difference between the placebo and the RCN groups is obviously not significant but the difference of the average gains between the MSP and the placebo groups was determined to be significant at the 5 per cent level. However, putting the men together in this manner and determining the average gain in mean score obscures the results to some extent.

Therefore, table 4 is of primary interest for it shows for each group the number of men according to their qualification on the control fire (column 1), the average score on the control day (column 2), the mean score on the test fire (column 3), the average gain (column 4), the standard error of the average gain (column 5), the standard deviation of the individual gains in score (column 6). In the top scoring class (Sharpshooter-Expert) neither MSP nor RCN differs significantly from the placebo in mean gains considering the standard error of the mean gains. Among the Marksman, however, there is a large and significant difference.

TABLE 3. MEAN SCORES BY MEDICATION GROUPS

	CONTROL FIRE	TEST FIRE	DIFFERENCE
Placebo.....	277.4	280.8	+3.4
RCN.....	284.3	287.4	+3.1
MSP.....	279.3	288.6	+9.6

TABLE 4. MEAN SCORES BY MARKSMANSHIP CLASSES

	1 NO. MEN	2 CONTROL FIRE	3 TEST FIRE	4 MEAN GAIN	5 S.E. MEAN GAIN	6 S.D. MEAN GAIN
<i>Expert-Sharpshooter</i>						
Placebo.....	20	297.4	293.4	-4.0	2.2	9.6
RCN.....	23	301.7	296.3	-5.4	2.2	12.5
MSP.....	21	297.4	304.8	+6.8	2.8	10.1
<i>Marksman</i>						
Placebo.....	28	279.7	282.0	+2.3	2.0	10.6
RCN.....	29	280.1	286.0	+5.9	2.3	12.0
MSP.....	28	279.0	291.0	+12.0	2.5	12.9
<i>Unqualified</i>						
Placebo.....	15	248.0	260.7	+12.7	5.4	20.1
RCN.....	9	249.0	268.0	+19.0	6.1	17.2
MSP.....	13	247.0	267.0	+20.0	6.0	20.8

Those taking MSP had an average gain of nearly 10 units higher than those taking a placebo. This difference would occur by chance only 4 times in 1000 trials<sup>4</sup>. The average gain in the unqualified categories for both RCN and MSP exceeded that for the placebo. Here, however, the standard errors were large due to the small numbers and to the fact that men who fail to qualify are more variable as to their individual gains than those who qualify.

<sup>4</sup> We are greatly indebted to Dr. Margaret Merrell of the Department of Biostatistics, The Johns Hopkins University, for the statistical analysis of much of this work.

It is also of interest that the difference between MSP and placebo, which was significant for the Marksman, is in the same direction for both the Expert-Sharpshooter categories and for the unqualified. The RCN group shows no such consistency in direction and in no case is the difference significant.

In table 5 the results of the second experiment are presented. It can be seen that the administration of 260 mg. of 'V-12' to expert riflemen had no effect on their rapid fire marksmanship.

TABLE 5. EFFECT OF V-12 ON MARKSMANSHIP OF EXPERTS

GROUP	NO. MEN	0650 MEDICATION	0745 FIRE (200 YD.)	0800 MEDICATION	0930 FIRE (200 YD.)	DIFFER- ENCE	1100 FIRE (300 YD.)
I	46	2 placebos	74.1	2 placebos	75.3	+1.2	72.0
II	51	2 placebos	73.9	4 gr. V-12	76.1	+2.2	71.8

## DISCUSSION

Grouping all men together without regard to the various classes and then determining the average gain obscures the results. This is due to a number of factors, one of which is that those who do well on a single test show only small gains or losses while the poorer and average marksmen have substantially greater opportunity for gains. Furthermore, analyzing the results on the basis of the various categories assures a more homogeneous group than the group as a whole. Of course, this also diminishes the standard error of the mean gain by the positive association in the control and test scores. The data treated in this manner show that the mean gain of the MSP group among those who qualified as Marksman on their control fire had a smaller probability of chance than if the results of all the classes were combined.

In view of the facts that: 1) the men were randomly distributed into the various medication groups; 2) the scores for the various groups were similar at the control tests; 3) the men were treated in the same way, the evidence reported here indicates that MSP in the dosage recommended for preventing motion sickness (2) has a definitely beneficial effect on marksmanship. This is more evident in average shots than in the top scoring and poorer classes. It is of interest to note that the average 10-point gain in marksmanship as a result of taking MSP is almost sufficient to qualify a man for the next higher classification.

On the other hand, there was no indication that any of the drugs tested had an adverse effect on the marksmanship of expert riflemen. Even in this class the MSP group exhibited a trend toward better scores than the placebo controls. It is apparent, therefore, that the belladonna alkaloids in the amounts and types present in these preparations had no measurable adverse effect on visual and motor efficiency as determined by marksmanship.

The question arises as to what components of the MSP preparation are

responsible for the improvement in marksmanship. Attempts to determine this were halted with the cessation of hostilities. The results indicate that it may be the amytal in the preparation. In this respect, it is noteworthy that RCN does not contain amytal and the findings with this preparation were neither consistent in direction nor were the differences significant in any instance. It is conceivable, therefore, that amytal, through a possible 'steady-ing action,' may be the agent responsible for this effect. Bearing on this point, it is of interest to note that in response to the query: "How did the pills make you feel?" 32 per cent of those taking the barbiturate preparation, 14 per cent of the RCN group and 9 per cent of the placebo group reported that it 'calmed' them, or words to that effect.

The results of this and other studies by Tyler (8) suggest interesting possibilities in the use of such drugs. There are combat situations that require men to perform their duties under conditions of excessive stress and fatigue. In many such situations the administration of a sedative may be more desirable than giving a stimulant. It has already been demonstrated by Tyler (8) that barbiturates can be given to men who stay awake for over a hundred hours without significantly affecting performance or their ability to stay awake.

#### SUMMARY

'MSP' (Motion Sickness Preventive, Army Development Type) had a definitely beneficial effect on marksmanship which was more pronounced on average shots. A similar trend was observed among top-scoring men (Sharpshooters and Experts). In this group, however, the gain was not outside the chance range. 'RCN' in dosages employed did not produce any consistent or significant gain in marksmanship. There was no indication, however, that this remedy interfered with this skill. 'V-12' did not produce any significant effect on the fire power of 'expert' marksmen.

The result of this and other studies (7, 8) indicate that MSP in the doses recommended as a preventive of motion sickness (2) can be safely given to military personnel.

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## *Application of Gray's Theory of Respiratory Control to the Hyperpnea Produced by Passive Movements of the Limbs<sup>1</sup>*

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THIS PAPER is an attempt to analyze the hyperpnea produced by so-called 'passive' movements of the limbs in terms of Gray's (1) multiple factor theory of respiratory control. Gray, himself, has made an approximate analysis of this phenomenon, but he did not have available the necessary data to make an exact application of his theory. Analysis of such a situation by this theory requires the following simultaneous information: 1) the alveolar (rather than the total) ventilation and 2) the arterial or alveolar carbon dioxide tension. Previous workers (2, 3) have made measurements of the ventilation but not of the  $p\text{CO}_2$ , and if there is no increase in metabolism the latter factor can be estimated from the former. On the other hand, if movement of the limbs by external forces involves an increase in metabolism, as is indicated by the experiments of Liljestrand and Stenstrom (4), the  $p\text{CO}_2$  must be directly measured.

### EXPERIMENTAL

*Series I.* The subject lay supine on a table which supported the whole body except the right leg below the knee. The right foot was strapped to a stirrup located at the end of a lever, the axis of which was in line with that of the knee joint. The lever could be driven by an electric motor in such a fashion that the lower leg was alternately extended and flexed through about 60 degrees of arc at a rate of 70 cycles per minute. After a 15-minute rest period the

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<sup>1</sup>Work done under contract recommended by Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester, and under contract with the Air Materiel Command, Wright Field.

subject breathed oxygen through a mouthpiece from a continuous circuit 12-liter recording spirometer equipped with a soda lime absorber and circulation pump. Continuous recording was made during the subsequent 25 minutes which were divided into 5 five-minute periods as follows: 1) normal breathing; 2) passive exercise; 3) recovery; 4) passive exercise; 5) recovery.

Experiments of this type were performed on 9 subjects. A summary of the results is shown in table 1. Only two subjects failed to show an increase in minute volume, and all subjects showed an increase in either volume or frequency of breathing during the exercise periods. All but one subject showed an increase of oxygen consumption during the 1st exercise period, and all showed an increase during the 2nd exercise period.

*Series II.* Since the above experiments indicated an increased metabolism, it seemed desirable to make measurements of alveolar gases during passive exercise. In a 2nd series of experiments, the subjects breathed air through

TABLE 1. SUMMARY OF EXPERIMENTS IN SERIES I

PERIODS	1	2	3	4	5
Frequency of breathing.....	100	150 $\pm$ 76	110 $\pm$ 28	199 $\pm$ 77	117 $\pm$ 41
Minute vol.....	100	143 $\pm$ 42	97 $\pm$ 13	140 $\pm$ 51	84 $\pm$ 19
Oxygen consumption.....	100	110 $\pm$ 11	108 $\pm$ 11	120 $\pm$ 10	107 $\pm$ 16

Column heads designate the consecutive 5-min. periods comprising the experiment: 1) normal breathing; 2) passive exercise; 3) recovery; 4) passive exercise; 5) recovery. All values are the averages for 9 subjects and are expressed as percentage of the normal control values. Standard deviations are indicated.

a face mask and expired through a gas meter which recorded the respiratory rate and volume. Alveolar oxygen and carbon dioxide tensions were obtained each minute by means of the automatic alveolar air sampler described by Rahn *et al.* (5). With this device the last few milliliters of each expiration are passed through a Cambridge Instrument Company CO<sub>2</sub> meter and a Pauling Oxygen Tensimeter. Following a 15-minute initial rest period, measurements were made during a 30-minute period consisting of 10 minutes normal, 10 minutes passive exercise and 10 minutes recovery.

*Series III.* A third series of experiments was similarly conducted except that the subject sat on a bicycle with his feet on the pedals. A motor was coupled to the rear wheel so that each pedal could be driven at a rate of fifty revolutions per minute.

## RESULTS

A summary of the average values for alveolar pCO<sub>2</sub>, pO<sub>2</sub> total ventilation and frequency of breathing observed in each period of Series II and III is given in table 2.

The results of all 3 types of experiments confirm the finding made by previous workers (2, 3) that movements of the limbs produced by external forces involve a considerable increase in the ventilation. In some individuals there is also an appreciable increase in oxygen consumption. This increased metabolism presumably indicates that the subjects were unable to be completely passive, but unconsciously resisted the applied forces to some degree. However, the simultaneous measurement of alveolar carbon dioxide tension

TABLE 2. AVERAGES OF MEASUREMENTS OF ALVEOLAR  $p\text{CO}_2$  AND  $p\text{O}_2$ , TOTAL VENTILATION, AND FREQUENCY OF BREATHING: ORIGINAL MEASUREMENTS WERE MADE EACH MINUTE DURING THE EXPERIMENT

Period	Subject	SERIES II				SERIES III			
		$p\text{CO}_2$	$p\text{O}_2$	Minute Vol.	Frequency of Breathing	$p\text{CO}_2$	$p\text{O}_2$	Minute Vol.	Frequency of Breathing
		mm. Hg.		l/min. BTPS		mm. Hg.		l/min. BTPS	
Control	R. S.	42.5	96.2	5.78	11.3	38.2	102.5	8.29	13.5
	H. R.	39.8	99.6	6.33	8.7	37.3	100.1	7.84	11.4
	I. E.	42.0	95.2	6.32	11.3	36.8	101.7	7.62	13.7
	R. O.	42.3	94.3	5.83	4.9	36.5	106.8	7.79	6.6
	A. O.	39.7	98.8	6.50	8.1	35.5	103.8	8.01	10.1
	R. D.	40.3	96.1	7.37	8.9	40.3	98.0	7.21	12.3
	Mean	41.1	96.7	6.35	8.9	37.4	102.2	7.79	11.3
Passive Exercise	R. S.	39.3	104.2	7.32	13.8	37.9	103.8	9.29	15.9
	H. R.	37.7	105.8	7.98	10.1	35.4	103.6	8.63	8.2
	I. E.	40.5	96.7	7.25	13.5	38.2	101.8	10.04	14.4
	R. O.	41.8	94.5	5.67	7.2	41.1	102.0	9.16	7.9
	A. O.	37.0	104.7	8.42	6.3	30.7	115.5	15.67	8.9
	R. D.	36.4	103.9	7.59	11.4	38.2	101.7	12.38	24.9
	Mean	38.8	101.6	7.37	10.4	36.9	104.7	10.86	13.4
Recovery	R. S.	40.5	100.9	6.11	11.6	38.3	102.09	7.80	13.7
	H. R.	39.2	96.9	5.33	7.0	37.4	98.30	7.52	10.3
	I. E.	41.7	94.3	5.99	11.6	36.1	103.01	7.19	13.6
	R. O.	41.2	96.2	6.34	7.1	38.1	103.27	7.03	5.5
	A. O.	39.2	94.9	6.00	8.7	34.2	93.70	5.86	8.5
	R. D.	36.5	101.7	6.70	10.6	39.1	100.07	6.84	16.8
	Mean	39.7	97.5	6.08	9.4	37.2	100.07	7.04	11.4

and ventilation makes it possible to estimate by Gray's theory the amount of ventilation due to the H-ion,  $p\text{CO}_2$  complex, and the amount due to the passive exercise *per se*, if it is assumed that these are the only respiratory stimuli involved, and that the bicarbonate capacity of the blood remains constant.

According to Gray's theory each of the various stimuli for respiration exerts its own independent effect, and the total stimulus is equal to the algebraic sum of the individual stimuli. In a normal resting individual the H-ion,  $p\text{CO}_2$  complex is assumed to be the only stimulus acting. From various se-



lected data showing the ventilatory response to breathing carbon dioxide mixtures, Gray has shown that the alveolar ventilation may be related to the alveolar  $p\text{CO}_2$  by the following equation, when the H-ion,  $p\text{CO}_2$  complex is the only stimulus for breathing. (Gray's equations require that the ventilation be expressed as a *ventilation ratio*, V.R., which is defined as the actual alveolar ventilation divided by the resting alveolar ventilation.)

$$\text{V.R.}_{\text{H},p\text{CO}_2} = 0.4 p\text{CO}_2 - 15 \quad (1)$$

The constants of the above equation require the normal resting alveolar  $p\text{CO}_2$  to be 40 mm.Hg. (The ventilation ratio, V.R., is unity under such conditions.) Since the resting alveolar  $p\text{CO}_2$  of our subjects was not exactly 40, we have adjusted the intercept constant of the above equation. In our second series of experiments the mean resting alveolar  $p\text{CO}_2$  was 41.1 mm. The mean alveolar ventilation during the same period was assumed to be due entirely to the H-ion,  $p\text{CO}_2$  complex and to have a V.R. value of unity. The new intercept constant was obtained as follows:  $1 = (0.4) (41.1) - K$ ;  $K = 15.44$

$$\text{V.R.}_{\text{H},p\text{CO}_2} = 0.4 p\text{CO}_2 - 15.44 \quad (2)$$

The actual alveolar ventilation was calculated in l/min. for each minute of the experiment for each subject from the observed total minute ventilation, frequency, and an estimated dead space (physiological plus mask) of 210 cc. In order to express the ventilation in terms of a *ventilation ratio*, each of the alveolar ventilation values thus obtained for a particular subject was then divided by the mean resting alveolar ventilation for that subject. A mean *ventilation ratio* for each minute of the experiment was then obtained by averaging all the individual V.R. values for each minute. The mean values are plotted as the solid line of figure 1. That part of the alveolar ventilation theoretically due to the H-ion,  $p\text{CO}_2$  complex was next calculated by inserting the mean  $p\text{CO}_2$  for all subjects for each minute of the experiment into equation 2. The values thus obtained were plotted to form the dotted line of figure 1.

A similar procedure was applied to the data of Series III, and the results are shown in figure 2. The formula used for computing the theoretical alveolar ventilation due to the H-ion,  $p\text{CO}_2$  complex in this series was

$$\text{V.R.}_{\text{H},p\text{CO}_2} = 0.4 p\text{CO}_2 - 13.96 \quad (3)$$

since the mean resting  $p\text{CO}_2$  was 37.4 mm. This resting value, which is considerably lower than that obtained in the second series, reflects the well-known effects of posture on the resting alveolar values, since the subjects were supine in the second series and sitting on a bicycle in the third series.

The mean alveolar respiratory quotient and oxygen consumption, as cal-

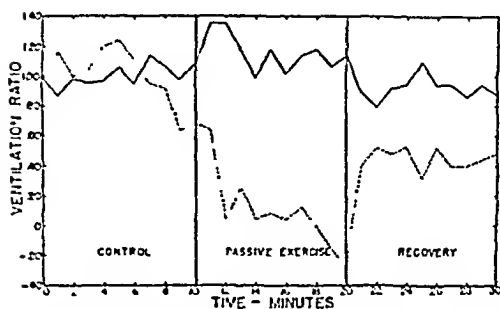


Fig. 1. EFFECT OF LIMB MOVEMENTS on alveolar ventilation in the experiments of Series II. The solid line indicates the actual alveolar ventilation as determined from the total and dead-space ventilations. The broken line indicates the amount of alveolar ventilation caused by the H-ion,  $p\text{CO}_2$  complex as calculated from Gray's equation. The vertical distance between the two curves at any time measures the amount of ventilation being stimulated by factors other than the H-ion,  $p\text{CO}_2$  complex. For example, at 18 minutes the actual alveolar ventilation is 1.18 in V.R. units (1.18 times the resting alveolar ventilation); the calculated stimulus value for  $(\text{H}, p\text{CO}_2)$  is 0. Therefore all the ventilation is due to some factor related to the limb movements. At 20 minutes the  $p\text{CO}_2$  has dropped so low that the calculated stimulus of  $(\text{H}, p\text{CO}_2)$  has a negative value, in other words an inhibition of 0.26 V.R. units. Since the actual ventilation is 1.14 V.R. units, the stimulus from the moving limbs must, according to the theory, be great enough to overcome this inhibition and in addition induce 1.14 V.R. units of ventilation. The stimulus from the moving limbs at this point is, therefore,  $1.14 + 0.26 = 1.40$ .

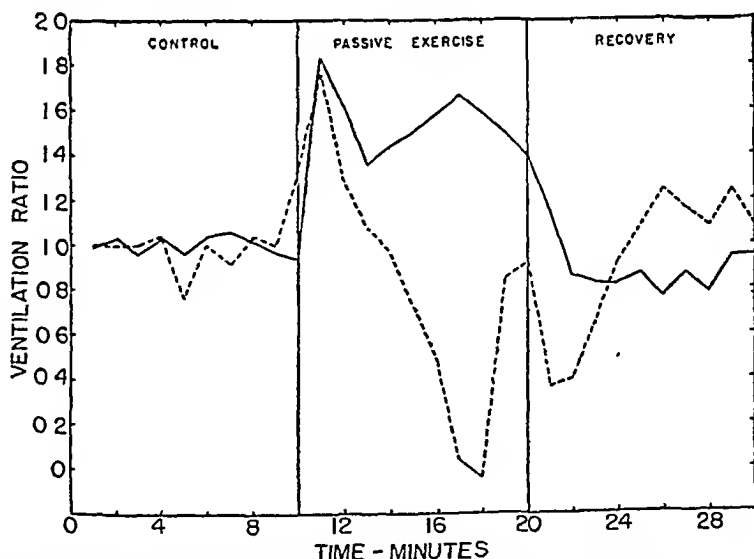


Fig. 2. EFFECT OF LIMB MOVEMENTS on alveolar ventilation in the experiments of Series III. For explanation see the legend for figure 1.

culated by use of equations 7 and 17 from Fenn, Rahn and Otis (6), for each minute of the experiments of Series II and III are plotted in figure 3.

The solid line in figures 1 and 2 indicates the actual alveolar ventilation and the dotted line the amount theoretically due to the prevailing  $\text{H}, p\text{CO}_2$ .

The vertical distance between these two curves at any instant represents stimulation or inhibition of the ventilation by other agents, presumably stimuli from the moving limbs. During the control periods of both experiments the alveolar ventilation remains relatively constant, and shows only random variation around a ventilation ratio of 1. When passive exercise begins there is an immediate increase in the ventilation which reaches a peak during the first or second minute. Thereafter, it declines, nearly to the resting value in Series II, but remains well above in Series III.

That portion of the alveolar ventilation theoretically due to  $(H, pCO_2)$  during the period of passive exercise is never as great as the actual ventilation

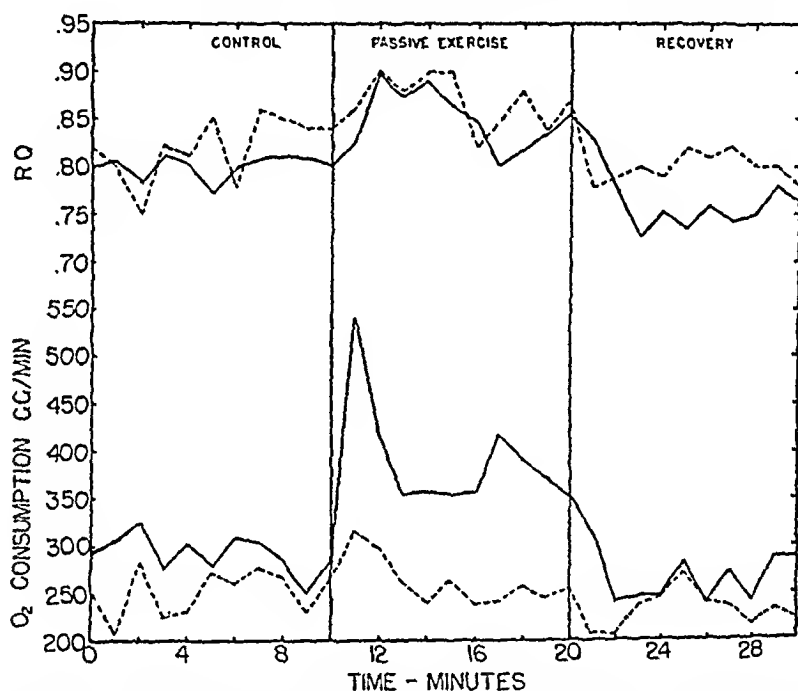


Fig. 3. OXYGEN CONSUMPTIONS and respiratory quotients calculated from the data of Series II (dotted lines) and Series III (solid lines).

except during the first minute of exercise in Series III. Although the actual ventilation remains above normal throughout the period of passive exercise, the partial stimulus of  $(H, pCO_2)$  becomes in general less and less and declines to a point where it is exerting no effect or is even inhibiting the ventilation. Correlated with this is the generally elevated R.Q. (fig. 3) which indicates the development of hypocapnia during this period. At the same time the stimulus from other agents (presumably something related to the moving limbs) generally increases throughout the period of passive exercise (except during the last two minutes of Series III), as indicated by the divergence of the dotted and solid lines of figures 2 and 3. This stimulus at times exerts an effect great enough to account for an increment of ventilation equivalent to 1.5 times the resting ventilation.

During the recovery period one would expect the ventilation to be due entirely to the H-ion,  $p\text{CO}_2$  complex and that the dotted and solid lines of figures 1 and 2 would converge. In figure 2, they do in fact have about the same average value, but in figure 1 they remain somewhat divergent and leave about 0.4 V.R. units of ventilation without explanation, unless one assumes some after discharge phenomenon or persistence of some chemical agent. The behavior of the R.Q. (fig. 3) during the recovery period is instructive. In Series III it is, on the average, depressed indicating retention of  $\text{CO}_2$  and recovery from the hypocapnia that developed during the exercise period. In Series II the R.Q. is less depressed and recovery is less complete.

The increased oxygen consumption observed during the exercise periods of Series I has already been mentioned. The oxygen consumption plotted in figure 3 for each minute of Series II and III shows a rise to a maximum during the first minute of exercise and a subsequent decline to a value that remains relatively constant after the third minute. In Series II this constant value is not significantly different from the resting consumption but in Series III it remains considerably elevated. It may be concluded that in Series III, at least, the limb movements were not entirely passive. The relatively high oxygen consumption during the first minute of exercise may be related to two factors. In the first place, the subject would probably tend to resist the applied force more when it first began than later after he became accustomed to it. Secondly, the movements might improve the venous return from the limbs and drive out blood that had pooled there during the preceding 15-minute rest period and 10-minute control. Such blood would probably be relatively deficient in oxygen and high in  $\text{CO}_2$ , and when it reached the lungs would cause an increased  $\text{O}_2$  consumption as well as an increased alveolar  $p\text{CO}_2$ . The amount of blood pooled would be much larger in Series III because the subjects were in the sitting position, and it is in this series that the most striking initial increase in oxygen consumption occurs as well as an increase in alveolar  $p\text{CO}_2$  (enough to account for nearly all the increased ventilation during the first minute).

Unpublished data obtained by Rahn in this laboratory indicate that when a subject who has been in the erect position on a tilt-board for some time is tilted to the supine position, the oxygen consumption may show an increase of 90 per cent during the first minute, due in part to displacement of blood from the limbs by the change of position. Much the same conditions probably hold in the experiments of Series III except that here the movements of the limbs serve to displace the pooled blood.

#### COMMENT

In summary, the above experiments indicate that movements of the limbs produced by external forces are not always entirely passive, but that

they may involve an increased oxygen consumption and carbon dioxide production. Furthermore, the possibility that such movements may introduce previously pooled blood into the general circulation must be considered. This effect would be especially important in experiments of only two or three minutes duration, such as those of Harrison *et al.* and of Comroe and Schmidt, because most of the blood displacement would probably occur early in the exercise period. Measurement of the alveolar or arterial  $p\text{CO}_2$  is therefore necessary to evaluate the stimulating effects of such movements on the respiration. When analyzed in terms of Gray's theory, the present experiments indicate that the stimulus from some factor associated with the moving limbs is great enough to produce a ventilation increment about equal to the resting ventilation. Gray's estimate of the magnitude of the stimulus from limb movements is about five times as great, but he assumed that there was no increase in metabolism.

The nature of the stimulus from the moving limbs is, of course, not identified by the present experiments, but there is much evidence that it is a reflex involving receptors in the joints (2, 3, 7, 8). The importance of such reflexes during *active* work is not generally agreed upon. Asmussen and Nielsen (9) believe that they are mainly responsible for the hyperpnea during light work, but that during heavy work (in which the blood lactate is increased) some unidentified chemical substance to which the arterial chemoreceptors are sensitive becomes more important. On the other hand, von Euler and Liljestrand (10) conclude that direct chemical stimulation of the respiratory center is the principal mechanism involved. Comroe's (11) opinion that no single factor theory will suffice is well borne out by the available evidence, although at present it is not possible to quantitatively evaluate all the factors involved.

To speculate briefly, perhaps an approach based on the assumption that at least a part of the hyperpnea of muscular exercise as it normally occurs is a conditioned response to a complex pattern of stimulus conditions would prove fruitful.

#### SUMMARY

The observation of previous workers that movements of the limbs produced by external forces cause an increase in the ventilation rate of human subjects is confirmed. In some individuals an increase in the oxygen consumption was observed, indicating that these maneuvers are not always entirely passive. Continuous measurement of the alveolar oxygen and carbon dioxide tensions made possible the calculation of the ventilatory stimulus due to the movements of the limbs per se by means of Gray's multiple factor theory. Such calculations show that the stimulus from such movements is

enough to produce a ventilation increment 100 per cent to 150 per cent of the resting ventilation.

I wish to make acknowledgment to members of Civilian Public Service unit No. 115-R who served as subjects and technicians during these experiments, to Miss Helen Jacobs for making some of the calculations, and to Dr. Hermann Rahn and Dr. W. O. Fenn for their critical advice.

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# *Voluntary Pressure Breathing at High Altitudes<sup>1</sup>*

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DURING THE WAR an emergency procedure for increasing altitude tolerance was suggested by Commoner (1) and was called Voluntary Pressure Breathing (VPB) or later Emergency Breathing Procedure. This procedure consisted in a quick inspiration followed for 2 seconds by the development of maximal intrapulmonary pressure with a closed glottis. At the end of this pressure period, the air in the chest was slowly expired. This cycle was repeated 12 or more times a minute. Theoretically, this increased pressure raised the mean oxygen pressure in the alveoli and so increased the saturation of the blood. This procedure was tested by Commoner in low-pressure chambers and in actual flights at 25,000 ft. and he found that it was possible to manipulate the airplane or carry out other routine procedures without the use of oxygen at this altitude provided the breathing was done according to his directions. In further practical tests Gemmill, Lillienthal and Riley (2) at Pensacola found a gain in altitude tolerance of 4000 feet and an improvement in conscious survival with VPB at 44,500 ft.

Following the publication of Commoner's report, we became interested in this subject and believed that most of the advantage attributed to VPB was actually due to the concomitant hyperventilation; see Chadwick *et al.* (3a). Houston *et al.* at Pensacola (4) and King *et al.* at Bethesda (5) came to similar conclusions. Commoner found no evidence of hyperventilation in the symptoms of his subjects but reported that the  $pH$  of the urine excreted during VPB was greater than normal.

In a later report, Commoner (6) reinvestigated the question and reported that hyperventilation was far worse than normal breathing on account of the severe acapnia which developed. It was evident that he permitted his subjects to increase their ventilation far too much so that the symptoms of acapnia were severe. The comparison was therefore invalid. This is true in general of most of the hyperventilation tests which have been made. It is indeed difficult even for experienced persons to attain an optimum degree of hyperventilation.

Some efforts to increase altitude tolerance by special breathing methods were also

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tried in Germany and these are described by Schoedel (7) in his chapter in the Fiat Review of German Science. He mentions two patterns 1) with inspiration emphasized (Schnapp-atmung) and 2) with expiration emphasized (mountain climber's breathing). In the discussion Niggemeyer is quoted as believing that the first type is beneficial only because it prevents excessive loss of  $\text{CO}_2$  but still increases the ventilation. Likewise Klostermann is quoted as stating that it is only the volume of the ventilation and not the pattern of the breathing which is responsible for the success. No actual data concerning the effectiveness of these procedures are available from this source.

During the war this subject was classified as 'confidential' and no review of VPB has yet been published. Since our own studies included careful measurements of the ventilation rate and the composition of the alveolar gas it seemed worthwhile to collect them in this paper for publication so that the rather important theoretical aspects of the problem can be clearly presented. Most of the other investigations of the procedure have involved merely service testing for military use and most of them have not included data on the actual degree of acapnia which was produced. All agree, however, in showing that this VPB procedure increases the saturation of the arterial blood as measured by the Millikan oximeter.

#### METHODS

Two series of experiments were carried out. In Series A there were 29 ascents in the pressure chamber to 18,000 ft. breathing air and 14 ascents to 42,000 ft. breathing oxygen. Thirteen subjects (one female) participated. Comparisons were made of VPB and hyperventilation (HV). In Series B there were 23 man runs to 25,000 ft. breathing air with somewhat more extensive measurements for the study of the causes of failure.

In the flights of Series A the subject adjusted his oximeter to 96 per cent saturation breathing air at ground level after a preliminary rest of 5 to 10 minutes and then began the 'ascent' at the rate of 5000 ft./min. After 10 to 15 minutes at the desired altitude with normal breathing (with  $\text{O}_2$  at 25,000 ft. or above) a similar period of 10 to 15 minutes of VPB was begun. Following VPB and a 5-minute rest period with normal regulation of breathing a final period of 10 to 15 minutes was tried with hyperventilation (HV). The oximeter was checked again after the descent. Throughout the flight, oximeter readings were taken at 1-minute intervals and continuous records of volume and frequency of breathing were made. Alveolar samples were taken frequently and analyzed in the chamber for  $\text{CO}_2$  by the Scholander technique. Other samples were taken at the end of each period for analysis afterwards on the Haldane gas analysis apparatus.

*Respiratory Circuit.* Figure 1 is a diagram of the respiratory circuit and recording apparatus used in all ascents to test VPB. The subject wore a mask, designed for pressure-breathing which was equipped with a glass pipe-stem mouth-piece. The mouth-piece communicated via a side-tube in the mask inlet with a recording manometer, described below, which made it possible to obtain a record of the amount of pressure applied, duration of compres-



sion, and rate of respiration. During VPB the subject closed his lips about the mouth-piece inside the mask and exerted pressure against the manometer.

The main mask inlet communicated directly with a slide valve similar to one seen by one of us at the Mayo Aero-Medical Unit, for taking samples of alveolar air (fig. 1).

The air or oxygen supply was led through a Pioneer demand regulator and into a gasometer (commercial type). The latter was equipped with an electrical contact which was tripped once for each complete revolution of the registering lever. These contacts were recorded together with those of a time marker on a smoked drum outside the low pressure chamber. The gasometer

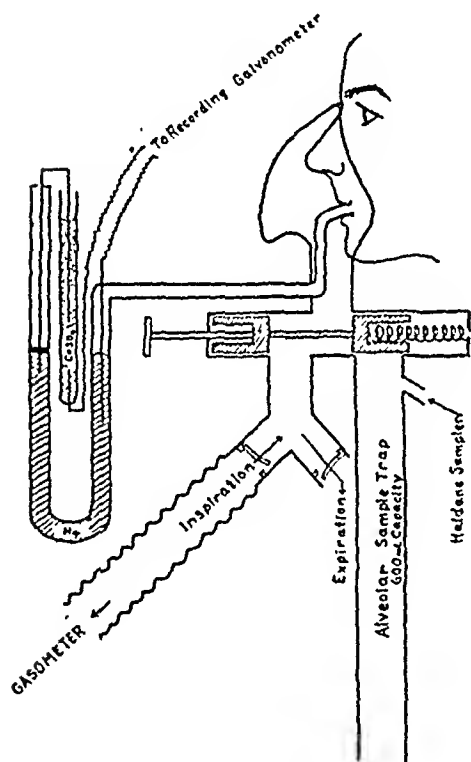


Fig. 1. APPARATUS USED for measuring the pressure developed in the lungs and for sampling the alveolar air.

lever made one revolution for approximately each 4.6 liters of gas which passed through. Inspired volumes were thus measured at ambient pressure and temperature, and were later corrected to  $37^{\circ}\text{C}$ ., saturated, at ambient pressure, it being assumed that the gas supplied was dry initially. From the gasometer, the supply was led to the mask inlet through a brass Y which carried flap valves for separating the inspired and expired air, and then through the sampling valve mentioned above. The apparatus dead-space from Y-valves to subject measured about 225 ml., with some individual variation depending on mask fit. The resistance to breathing through the circuit amounted to about  $-4$  cm. water on inspiration and  $+1$  cm. water on expiration, measured at the mask inlet at ground level. At altitude the resistance was considerably less. Tests were made before and during each experiment for possible leaks.

*Recording Manometer.* A float in the open arm of a U-tube mercury manometer carried a wire which dipped into a column of dilute copper sulphate solution (fig. 1). Leads from the wire and an electrode sealed into the bottom of the copper sulphate column were connected in series with a dry cell and an Esterline-Angus recording galvanometer.<sup>2</sup> The length of copper sulphate column in the electrical circuit varied as the float rose and fell with changes of pressure in the mercury manometer, thus causing changes in electrical resistance and in the galvanometer deflections.

*Sampling of Alveolar Air.* At the end of a normal expiration, the subject depressed the plunger of the slide valve (fig. 1) thus establishing communication between the mask inlet and sample trap and cutting himself off from the ordinary pathway of inspiration and expiration. He then made a forced expiration into the sample trap, which consisted of a 4-foot length of wide-bore rubber tubing with a capacity of 600 ml. After the forced expiration was completed, the plunger of the slide valve was released, and the subject was free to proceed with his breathing. He then released the clip on the side tube of the sampling trap and signalled to the operator outside the pressure chamber. The latter drew the sample into an evacuated sampling bottle over mercury. The tube connecting the sampling trap with the outlet on the tank wall was of only a few ml. capacity, and was washed out with alveolar air before the first sample was drawn. Sampling tubes of 80 ml. and 240 ml. capacity were used at 18,000 ft. and 42,000 ft., respectively. Check experiments showed that use of the larger tubes did not result in any dilution of the sample with tank air entering the lower end of the sampling trap. The samples were analyzed in duplicate for CO<sub>2</sub> (and for O<sub>2</sub> in 10 runs at 18,000 ft.) in an 11 ml. Haldane burette. For samples containing more than 30 per cent CO<sub>2</sub> (as was usual at 42,000 ft.) it was necessary to draw about 7.5 ml. of sample into the burette, measure its volume accurately, and then dilute it with a measured amount of air or nitrogen to make a total volume of 10 to 11 ml., before proceeding with the analysis. This procedure introduces extra possibilities of error in the analyses, but duplicate analyses were run routinely and checked to within 0.1 per cent CO<sub>2</sub>, a degree of accuracy quite sufficient for the purposes of these experiments. (At 42,000 ft., a difference of 0.1% CO<sub>2</sub> in the analyses amounts to only 0.081 mm. Hg.)

## RESULTS

### *VPB and HV at 18,000 and 42,000 feet (Series A)*

The data from these experiments are summarized in table 1. The complete data will be found in tables 3 and 5 of our original report (3) which are not reproduced here. The general trend of these averages at 18,000 ft. is

<sup>2</sup> We are indebted to Dr. R. B. Dean for the design of this recording manometer.

TABLE 1. COMPARISON OF NORMAL BREATHING, N, VOLUNTARY PRESSURE BREATHING, VPB, AND HYPERVENTILATION, HV, AT ALTITUDE. AVERAGE VALUES

TYPE OF BREATHING	ALVEOLAR pCO <sub>2</sub>	ALVEOLAR pO <sub>2</sub>	ALVEOLAR R.Q.	HbO <sub>2</sub>	VENTILATION
18,000 ft. (10 exper., 7 subjects)					
N	mm. Hg 32.8	mm. Hg 34.9	.94	% 81.7	l/min. 14.0
VPB	24.0	51.7	1.10	88.8	22.7
N	28.1	36.6	.82	82.1	13.0
HV	18.9	51.7	1.08	91.0	26.9
18,000 ft. (19 exper., 10 subjects)					
N	30.7			78.0	16.6
VPB	26.6			83.0	22.5
HV	21.8			88.6	29.4
42,000 ft. (13 exper., 8 subjects)					
N	32.5	48.5 <sup>1</sup>		81.2	16.1
VPB	31.4	65.8		89.5	22.8
HV	20.9	60.1		91.0	28.7

<sup>1</sup> Obtained by subtraction = (B-47 - pCO<sub>2</sub>).

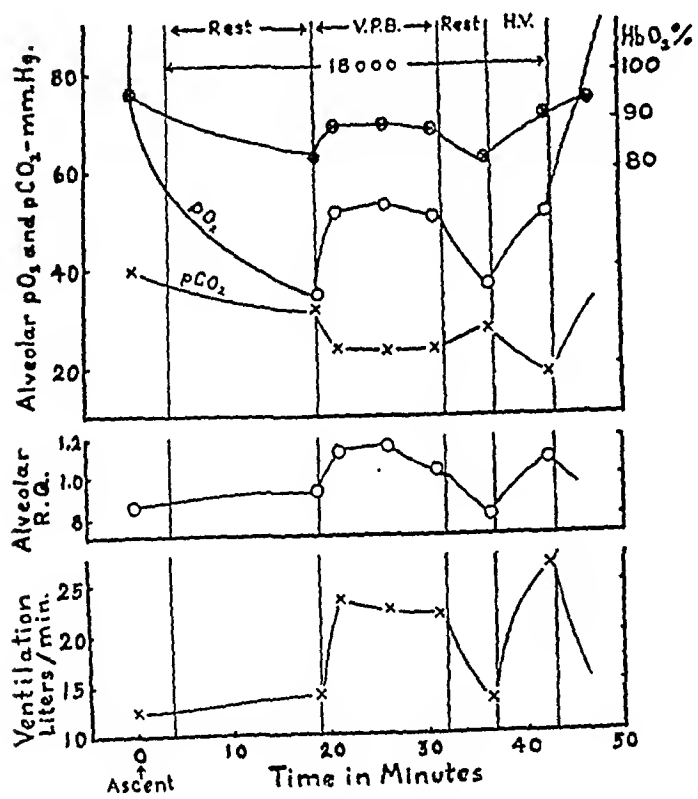


Fig. 2. AVERAGE VALUES OBTAINED in simulated flights to 18,000 ft. breathing air through a gasometer and gas mask and using voluntary pressure breathing and hyperventilation without pressure in alternation with normal breathing.

shown in figure 2 which illustrates the way in which the various quantities varied with time in the course of an experiment. In 19 of the 29 experiments no measurements were made of alveolar  $pO_2$  and these were averaged in table 1 separately from the other 10 experiments. Three successive samples were taken during VPB but only one during HV. The 3 VPB samples agreed very closely and are averaged together. It is evident that  $pCO_2$  is low and  $pO_2$ , ventilation, percentage saturation and R.Q. are all high compared to the normal, during both VPB and HV. The rise in the percentage saturation confirms the findings of Commoner (1) and all other workers in this field. This table shows in addition that there is very little difference between VPB and HV in any of the quantities measured. The agreement of course depends upon the proper adjustment of the ventilation rates obtained in the two cases. On the whole, in HV the  $pCO_2$  was somewhat lower and the ventilation and saturation somewhat higher than in VPB.

The relation between hyperventilation and VPB is shown in figure 3 in which the change in alveolar  $pO_2$  is plotted against the change in  $pCO_2$  which resulted from the procedure employed. The 10 experiments here illustrated are those at 18,000 ft. in which analyses were made for both  $O_2$  and  $CO_2$ , so that the values are quite independent of one another. The two sets of points for hyperventilation (crosses) and VPB (circles) have been fitted by regression lines by the method of least squares. The two lines have nearly identical slopes, these being a measure of the gain in  $pO_2$  brought about by the lowering of the  $pCO_2$ . The vertical distance between the two lines represents the gain in  $pO_2$  which resulted from the application of pressure provided the ventilation rate was maintained at such a level that the mean  $pCO_2$  remained unchanged. In order to do this, the ventilation rate must be a little larger with VPB than in VH without pressure and the  $pCO_2$  in the lungs during expiration, i.e., when the pressure is released, must be a little lower to compensate for the increase in  $pCO_2$  which occurs, when pressure is applied. Evidently for most of the points, the gain in  $pO_2$  due to the application of pressure is small compared to the total gain. The actual magnitude of this gain due to pressure is about 5.5 mm. Hg of  $O_2$  tension (at a given  $pCO_2$ ). Considering the scatter of points this does not differ significantly from the gain to be expected from the mean pressure of 21.7 mm. which was applied, the theoretical value being  $21.7 \times 0.209$  or 4.5 mm. Hg.<sup>3</sup>

A similar curve can be plotted for the data at 42,000 ft. but in this case the  $pO_2$  values were merely calculated from the  $pCO_2$  values by difference since there were no other gases present. All the hyperventilation points, therefore, necessarily fall along a single straight line with a slope of  $45^\circ$  and the VPB

<sup>3</sup> The basis for this calculation is explained further below. The fraction of oxygen in the inspired air is 0.209. The mean pressure of 21.7 mm. was calculated from the average peak pressure of 54.3 mm. on the assumption that it was applied for 2 seconds out of 5 or 0.4 of the time.

points deviate from this line at corresponding  $p\text{CO}_2$  values only in proportion to the mean applied pulmonary pressure which varied around the average value of 16 mm. (range 8–26 mm.).

This average pressure developed in the VPB technique at 42,000 ft. is slightly less than the average pressure developed at 18,000 feet (29 exper.) which was 19.6 mm. (range 9–30 mm.). This difference is due to the lower ambient pressure at altitude which permits a greater diminution in volume for a given applied pressure. In carrying out the VPB maneuver at altitude it is noticeable that the chest collapses more when pressure is applied than it does at ground level. Rahn *et al.* (8) have calculated the magnitude of this collapse and have shown that with smaller chest volumes there is a progressive decrease in the magnitude of the maximum expiratory pressure which can be developed.

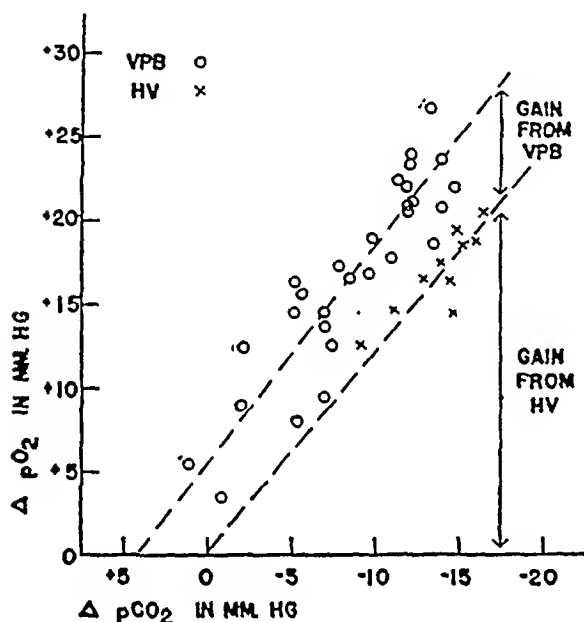


Fig. 3. SUMMARY OF 10 EXPERIMENTS simulated flights to 18,000 ft. in which a comparison was made between VPB (circles) and hyperventilation (crosses). The changes in alveolar oxygen tension thus produced (compared to the normal) are plotted against the corresponding changes in alveolar  $\text{CO}_2$  tension. All values during VPB have been corrected for the pressure which was applied so that the figures plotted represent the actual mean increment in partial pressure of the gas.

In theory, VPB should be far more effective in raising the alveolar  $p\text{O}_2$  when pure  $\text{O}_2$  is breathed, as at 42,000 ft. because under such conditions all of the pressure is divided between  $p\text{CO}_2$  and  $p\text{O}_2$ . From the data in table 1 for 42,000 ft. it can be calculated that the sum of  $p\text{O}_2$  and  $p\text{CO}_2$  increases 16 mm. above normal when VPB is used. At 18,000 ft. on the other hand, the added pulmonary pressure is divided between  $p\text{O}_2$ ,  $p\text{CO}_2$ , and  $p\text{N}_2$  in proportion to their several values. Unfortunately the  $\text{N}_2$  has a concentration of around 80 per cent so that only 20 per cent of the pressure is left to divide between  $p\text{O}_2$  and  $p\text{CO}_2$ . Thus from the data for 10 experiments at 18,000 feet in table 1 it can be calculated that the sum of  $p\text{O}_2$  and  $p\text{CO}_2$  increases in VPB by 8 mm. above the normal. This is greater than 20 per cent of the applied pressure of 21.7 mm. which is only 4.3 mm. The difference is due to the dilution of nitrogen at high R.Q. values which we have discussed elsewhere (9).

This high R.Q. in turn is due to the hyperventilation which accompanies VPB. The same amount of hyperventilation at 42,000 ft. is less effective in raising the  $pO_2$  because of the absence of nitrogen in the inspired air. The increased ventilation of the VPB tends therefore to obscure the greater theoretical effectiveness of this procedure at oxygen-breathing as compared to air-breathing altitudes.

From the figures for 18,000 ft. in table 1 it can be seen that VPB provides no greater alveolar  $pO_2$  than does HV but it does give a  $pCO_2$  which is greater by 5.1 mm. At 42,000 ft. both  $pO_2$  and  $pCO_2$  are higher with VPB than with HV. At this level it is interesting to note that in comparison to the normal, VPB causes almost no change in the  $pCO_2$  but is all applied to an increase of 17.3 mm. in the  $pO_2$ . In this connection it may appear strange that the ventilation at 42,000 ft. increases with VPB from a normal of 16.1 to 22.8 l/min. while the  $pCO_2$  shows almost no change. It should be remembered that the ventilation is measured at ambient pressure while the  $pCO_2$  and  $pO_2$  values are corrected for the mean pressure in the lungs which is voluntarily elevated by the subject. Because of this applied pressure the actual mean  $pCO_2$  in the alveoli does not fall in spite of the increased ventilation. In addition the metabolic rate has been increased some 45 per cent as will be shown below.

#### *VPB and HV at 25,000 feet (Series B)*

For practical purposes it is more important to test any emergency breathing procedure at an altitude of 25,000 ft. where only a few persons are able to maintain consciousness without special instructions. Any benefit of VPB or HV may therefore be expected to become evident in terms of better survival. The experiments at 25,000 ft. were very similar to those of Series A except that we did not usually test both VPB and HV in the same flight. It will be convenient, therefore, to report the HV and the VPB flights separately.

The apparatus was very similar to that described in figure 1 except that the gasometer was placed in the output rather than the intake side of the mask and the expired air was sampled beyond the gasometer and analyzed continuously by passing it through a Pauling oxygen tensimeter and a Cambridge Instrument Company carbon dioxide meter (thermal conductivity). Respiratory rates were recorded by means of an electrical contact activated by inspiratory and expiratory mask pressures. These contacts together with those made by the revolutions of the gasometer were recorded outside the chamber by pens writing on a moving paper strip. Not all of these measurements were made in all experiments.

*Hyperventilation with Air.* Instructions to our subjects before ascent were simply to 'hyperventilate, but not excessively' after they were shunted from oxygen to air at an altitude of 25,000 ft. The control of the rate and depth of breathing was left entirely to their own judgment. During this performance

they were required to write more or less continuously in order to provide reliable criteria of their performance. When subjects showed signs of failing they were encouraged by commands from observers to maintain their breathing. In cases of lack of response to questions, illegible handwriting or convulsive breathing, subjects were returned to oxygen where they immediately recovered. Such flights are designated as 'unsuccessful'. In a 'successful' flight the subject was able to maintain normal responses and handwriting for a period of 17 to 35 minutes.

In the hyperventilation series two types of runs were made. 1) Only oximeter and handwriting records were required. This effort to eliminate all other instrumentation was made in order to reduce breathing resistance to a minimum. This includes flights nos. 268 to 277 inclusive. 2) A full set of recordings was accomplished. It should be borne in mind that this equipment caused a greater resistance to breathing than would normally occur. This resistance was produced primarily by the special slide valve for sampling alveolar gases, the gasometer, and the relatively long pieces of tubing.

Of the 14 subjects engaging in these flights 8 succeeded while 6 failed. Three of the successful subjects repeated the run at another time successfully. Three of the unsuccessful subjects repeated the run one to three times and failed in all attempts. Altogether we have observations on 11 successful runs and 12 unsuccessful runs. The unsuccessful runs lasted on the average 6 minutes (range 4-15). The successful flights were terminated on the average in 28 minutes (range 17-35), but in each instance the subject wanted to continue and was considered in 'good' shape by his observers. These subjects all "felt as if they could have gone on forever."

A comparison of the successful and the unsuccessful flights is given in table 2. The data are more fragmentary in the unsuccessful flights which were terminated early and it is difficult to be certain of the cause of failure in all cases. On the average however it may be seen that the ventilation was slightly greater in the successful flights, being in all cases over 30 l/min. In at least 6 of the unsuccessful flights the ventilation was below 30. Likewise on the average in the successful flights the alveolar  $p\text{CO}_2$  was lower both before and during the hyperventilation than in the flights that failed. This suggests that hyperventilation was at least one of the predisposing causes although there are some individual exceptions. In the unsuccessful flights the oximeter reading was always falling at the time the experiment was terminated and would presumably have gone lower than the last recorded figure if oxygen had not been supplied.

It is probably significant that those who failed did so repeatedly while those who were successful were likewise able to repeat their performance at will. It is not unlikely therefore that those who failed did so because of some special sensitivity to anoxia or acapnia rather than any inability to carry out

the technique properly. As indicated in table 5 about 50 per cent of all subjects are unable to retain consciousness at 25,000 feet by any type of breathing.

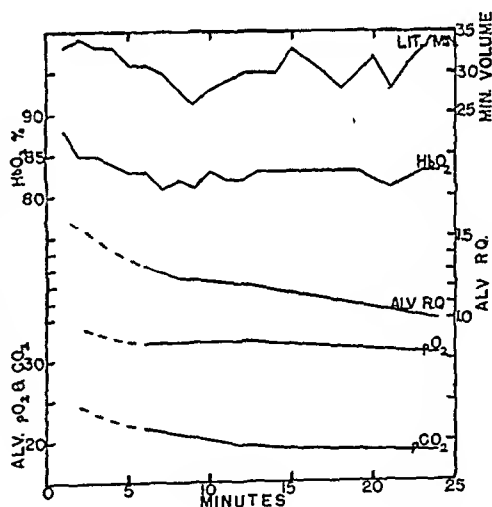
A graphical summary of the time course of the respiratory data from the successful flights to 25,000 feet with hyperventilation is shown in figure 4. It will be seen that the minute volume was about 30 l/min. and the arterial

TABLE 2. COMPARISON OF SUCCESSFUL AND UNSUCCESSFUL FLIGHTS ON HYPERVENTILATION AT 25,000 FEET

	SUCCESSFUL FLIGHTS	UNSUCCESSFUL FLIGHTS
Ventilation on O <sub>2</sub> before HV-1/min.	15	15
Ventilation on air-HV-1/min.	32.5 ± 4.6 (123)	30 ± 8.8 (29)
Duration of flight-min.	17-35 (+)	4-15
Terminal saturation-HbO <sub>2</sub> %	85 ± 4 (11)	77 ± 5 (12)
Alveolar pCO <sub>2</sub> before HV mm. Hg	33.3	37.5
Alveolar pCO <sub>2</sub> during HV mm. Hg	19.6 ± 3 (15)	26.2 (2)
Alveolar pCO <sub>2</sub> during HV mm. Hg	31.7 ± 2.0 (13)	30.0 (1)
Number of subjects	8	6
Number of flights	11	12

Figures in ( ) indicate number of figures averaged. Standard deviations are given where possible.

Fig. 4. AVERAGE VALUES OBTAINED in successful flights using hyperventilation on air at 25,000 ft. plotted against time measured from the beginning of the exposure. Each point is the average of 6 to 11 experiments and subjects. The same experiments and subjects are not represented in the figures for all the quantities plotted. Minute volumes in liters B.T.P.S. Hemoglobin saturations are based on analyses of alveolar air by the Haldane method in 8 experiments.



saturation above 80 per cent. The pO<sub>2</sub> was 31 mm. and the pCO<sub>2</sub> 19 mm. which according to Henderson's nomogram for the blood of A.V.B. should give an arterial saturation of about 75 per cent (instead of 82% as found). It is noteworthy that the R.Q. falls gradually during the hyperventilation, but remains above 1.0 for 24 minutes. For a period of this duration the maintenance of a high R.Q. is a factor of some importance for survival.



*Voluntary Pressure Breathing with Air.* The technique of this procedure was essentially the same as in our previous experiments except that greater pressure was applied by the abdominal muscles and less by the thoracic muscles and there was a greater inflation of the chest and a greater ventilation. These changes resulted from a visit from Dr. Commoner who endeavored to coach our subjects in his particular technique. The pressure was exerted against a mercury manometer through a pipe stem held in the mouth and was maintained (when possible) for 2 out of 5 seconds. Seven subjects attempted this procedure and three were successful, in maintaining consciousness for 17 to

TABLE 3. VOLUNTARY PRESSURE BREATHING AT 25,000 FEET

FLIGHT NO.	TIME ON AIR	MEAN PULM. PRES.	HbO <sub>2</sub>	VENT.	EXPIRED CO <sub>2</sub>	EXPIRED O <sub>2</sub>	CO <sub>2</sub> OUTPUT	O <sub>2</sub> INTAKE	EXPIRED R.Q.	ALVEOLAR AIR		
										pCO <sub>2</sub>	pO <sub>2</sub>	R.Q.
Successful Flights												
	min.	mm. Hg	%	l/min.	%	%	cc/min.			mm. Hg		
323	5	20	94							22.0	34.2	1.20
	15		90	38.1	7.92	14.16	657	532	1.23			
	20	12	90	48.6	7.57	13.51	803	774	1.04	22.0	33.1	1.25
	30	12	90	34.9	7.19	14.81	545	443	1.23	22.0	30.8	1.07
325	6	10 <sup>1</sup>	85	25.7	7.50	15.64	420	260	1.61	23.6	35.2	1.69
	12-19	12 <sup>1</sup>	77-82	31.2	7.26	14.99	494	440	1.12	22.4	33.4	1.30
	25-30	20	83	28.9	7.06	13.75	445	450	.99		33.0	
328	5-8	7 <sup>1</sup>	82-77	28.0	6.04	16.23	368	254	1.45	24.2	27.5	1.06
	16	10 <sup>1</sup>	77	55.1	7.05	16.67	845	411	2.05		31.8	
	25-29	10	78	61.0	7.50	15.99	1000	560	1.78	22.3	26.4	0.88
Averages		12	84	39.0	7.23	15.07	620	458	1.39	22.6	31.7	1.21
Miscellaneous Flights												
324 <sup>2</sup>	5	20	69	48.2	4.65	15.63	489	565	0.87	21.2		
327 <sup>3</sup>	9 (+27)	30	71		5.54	15.0	474	515	0.92	20.6	30.7	0.80
322 <sup>3</sup>	5 (+30)	30	85	39.5						20.0	29.3	0.72

<sup>1</sup> Approximate values.    <sup>2</sup> Unsuccessful flight.    <sup>3</sup> VPB at end of hyperventilation flight.

35 minutes. It is of some interest that only those succeeded who were also successful with straight hyperventilation. Of the 4 failures in this group 2 succeeded with hyperventilation while the other 2 did not. It is difficult to say to what the failures were due. At the beginning of VPB all our subjects developed a peak pressure of about 100 mm. In the unsuccessful flights a fairly good mean pressure was recorded because the subjects had to give up VPB and take oxygen before they had time to tire of the procedure. Of the 3 successful subjects one held his pressure faithfully for 2 seconds but the pressure so maintained was not very high; one developed a higher peak pressure but was unable to maintain it for 2 seconds; and the third was able to exert a

pressure only once every fourth breath so that the mean pressure was low. The ventilation was perhaps a little lower in the unsuccessful flights (28 as compared to 30.2 l/min.) and the percentage saturation just before collapse was 70 per cent as compared to 85 per cent in the successful flights. It appeared that the severe anoxia at 25,000 ft. weakened the determination to continue the development of pressure and made the VPB procedure more difficult than it seemed to be at 18,000 feet.

Detailed data for the three successful VPB flights at 25,000 ft. are given in table 3 together with data from one unsuccessful flight and two flights in which VPB was tried after 30 minutes of HV.

The most significant fact about this table is the low  $p\text{CO}_2$  value of 22.6 mm. Hg in the alveolar air and the high R.Q. of 1.39 due to the overventilation. Thus an average arterial saturation of 84 per cent was recorded in spite of the low  $p\text{O}_2$  of 31.7 mm. in the alveolar air. The figures for the oxygen consumption will be referred to later.

An altitude of 25,000 ft. is a critical one for survival since only 50 per cent of all subjects are able to maintain consciousness (table 5). Hence, the value of 31.7 mm. for the  $p\text{O}_2$  in the alveoli in the successful subjects supports the idea that 30 mm. is approximately the irreducible minimum for conscious survival.

### *Increased Oxygen Consumption Due to VPB*

It seems obvious that the strenuous effort required for the VPB procedure will considerably increase the need for oxygen. There is danger therefore that any increase in the alveolar oxygen tension which may result from the pressure applied will be more than offset by the increased amount of oxygen which must be driven into the blood and tissues. To investigate this question we made use of the Sanborn metabolism machine in some experiments at ground level. The subject wore a mask which could be connected by a 3-way stopcock either to the room air or to the apparatus. In the Sanborn apparatus the gases are circulated by a fan but to avoid all possibility of rebreathing expired air it was necessary to insert inspiratory and expiratory valves between the stopcock and the spirometer circuit. The experiment began with the subject sitting at rest for 5 to 10 minutes breathing through the mask to room air. Then the stopcock was turned to the spirometer and a record was taken for 8 minutes, for the determination of the resting rate of oxygen consumption. At the close of this record VPB was started and 4 minutes later another 6-minute record was taken. The purpose of the 4-minute wait was to avoid any false oxygen uptake due to increased  $p\text{O}_2$  in the lungs (as a result of hyperventilation) or due to increased mean saturation of the blood with oxygen (Bohr effect at lowered  $p\text{CO}_2$ ). Previous experiments (unpublished) had shown that after 4 minutes this false intake (amounting to some 40 cc.) was largely

complete and the rate of oxygen consumption had returned approximately to its true metabolic level.

Records were obtained with this technique on 12 subjects: (11 male, and 1 female), all of whom had been used in VPB ascents. The results are conclusive and confirm our supposition that the oxygen uptake increases considerably during VPB, due to the work involved. The data are summarized in table 4, which gives the individual results and averages for the group. Here it is seen that VPB at an average maximum pressure of 51.8 mm. Hg increases the oxygen consumption 45.5 per cent over rest, on the average. All subjects showed an increase, ranging from 20.7 per cent to 91.0 per cent. This experiment also shows that at a rate of 10.9 breaths/min. the subject, although

TABLE 4. EFFECT OF VPB ON RATE OF OXYGEN CONSUMPTION

SUBJECT	REST			VPB				INCREASE IN O <sub>2</sub> USED
	O <sub>2</sub> used	RATE MIN <sup>-1</sup>	VENTILA- TION	O <sub>2</sub> USED	RATE MIN <sup>-1</sup>	VENTILA- TION	PEAK PRESSURE	
	ml/min.		l/min.	ml/min.		l/min.	mm. Hg	%
1	310	14	14.8	530	14	20.0	65	70.9
2	260	12	9.7	380	13	21.4	50	46.1
3	295	11	8.0	430	13	28.9	60	45.7
4	290	14	12.1	390	13	12.1	50	34.5
5	260	13	7.4	390	10	22.7	52	50.0
6	220	11	10.2	420	10	22.7	52	91.0
7	300	14	10.3	410	12	19.4	48	36.6
8	285	18	11.2	480	12	15.9	65	68.5
9	290	17	8.7	370	9	15.1	45	27.6
10	240	10	6.2	290	10	10.3	47	20.8
11	370	15	8.1	495	7	9.8	45	33.8
12	290	15	8.9	350	8	13.3	45	20.7
Average	285	13.7	9.6	412	10.9	16.4	51.8	45.5

he was instructed not to increase his minute volume, will on the average do so by 6.8 liters. The same amount of voluntary hyperventilation without pressure would require an increase in oxygen consumption of only 7.1 cc/min. (10), or 3 per cent of the resting value. Therefore, it can be said that the application of pressure, chiefly by the abdominal muscles, was responsible for 93.5 per cent of the increase in oxygen uptake that took place in these experiments.

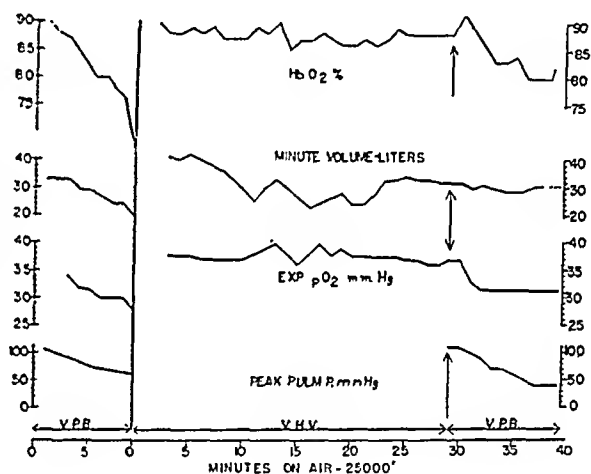
In table 3 some figures are given for the rates of oxygen consumption and CO<sub>2</sub> output during VPB at 25,000 ft. These values were calculated from the percentage composition of the expired air and the ventilation rates in l/min. The average rate of oxygen consumption in these 3 experiments was 458 cc/min. which is about 50 per cent higher than a normal rate of 300 cc/min. for a resting man. Since there were no resting values on these same subjects,

however, this can hardly be regarded as a rigorous confirmation of our ground level determinations.

Further confirmation of these results may be obtained by calculating the rates of oxygen consumption from the alveolar air data of table 1 of the 25,000-ft. flights using the alveolar air equation (9). The results show a 31 per cent increase due to VPB and a 23 per cent increase due to HV. These figures, however, may be partially explained by an increase in the dead space which was assumed to have a constant value of 360 cc. Because of this uncertainty the results are not presented in detail.

One further confirmation of the importance of the increased rate of oxygen consumption in VPB as compared to HV is shown in the graphs from *subject C.G.B.* in flight 327 which are shown in figure 5. In this experiment the sub-

Fig. 5. DATA OF FLIGHT 327 in which subject C.G.B. tested VPB and voluntary hyperventilation (VHV) at 25,000 ft. A recovery period on oxygen intervened between the first period on VPB and the period on VHV. See text.



ject started at 25,000 ft. with the VPB procedure and was able to maintain a good mean pulmonary pressure but the minute volume fell so low that he collapsed in 10 minutes from desaturation of the blood and resulting anoxia, with an expired  $pO_2$  less than 30 mm. After a short recovery period on oxygen the subject began to hyperventilate on air and continued this successfully for 20 minutes with a satisfactorily high oxygen tension of 37 mm. in the expired air and an arterial saturation of 87 per cent as indicated by the ear oximeter. At the end of this period of HV the subject again began VPB with the result that his arterial saturation and the  $pO_2$  of his expired air decreased markedly without much change in his minute ventilation volume. This occurred in spite of the increased pulmonary pressure and can only have been due to the increased utilization of oxygen. The temporary increase in the arterial saturation was due to the increased pulmonary pressure acting before the rate of oxygen consumption had increased to its new level. If the rate of oxygen

consumption is calculated from the oxygen content of the expired air and the ventilation volume it is found that the rate was 463 cc/min. during HV and 589 cc/min. during VPB. If we assume arbitrarily that HV required a 15 per cent increase over normal then the figure for VPB represents a 46 per cent increase which is in good agreement with our other values.

In a previous (unpublished) report we have shown that the elastic work of breathing is given by the expression  $W = \frac{fKT^2}{2} \times 10^{-5}$  where  $f$  is the number of breaths per minute,  $T$  is the tidal volume in cc.,  $K$  is the slope of the relaxation pressure curve,  $\frac{dp}{dT}$  ( $p$  is measured in cm.  $H_2O$ ) and  $W$  is the work per minute in kg. m. Using this formula and a value of  $K = 0.01$  it can be calculated that the elastic work of breathing is 0.34 kg. m. per min. for normal breathing at rest and 2.9 for hyperventilation at a frequency of 12/min. and a volume of 22.8 l/min. If at the same time the subject stops at each inspiration with a total lung volume of 4000 cc. and develops a pressure of 52 mm. Hg or 70 cm.  $H_2O$  the potential energy stored in this compressed air amounts to  $\frac{52}{(760-47)} \times$

$4000 \times \frac{70}{2} \times 12 = 1.22$  kg. m./min. This represents a 41 per cent increase in the work performed. In this estimate the work of moving the air against viscous resistance and turbulence has not been considered but this would not increase the work without pressure development more than perhaps 20 per cent (unpublished data). If this extra work of VPB is done with 5 per cent efficiency like the normal respiration (11) then it should require an extra 11.5 cc.  $O_2$ /min. which is the approximate energy equivalent of  $\frac{100}{5} \times 1.22$  kg. m.

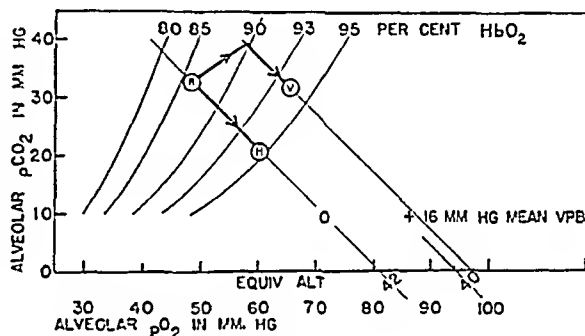
Since the extra oxygen actually used was more than 10 times this amount it is evident that the efficiency of the actual work done in VPB is exceedingly small. Presumably the effort represents a nearly maximal isometric contraction of all the muscles of the trunk exerting pressure against one another. It must be regarded, therefore, as a rather expensive compensatory mechanism. It might be noted that the above calculation is for VPB at ground level. At altitudes the work of developing pressure becomes greater because the lung volume is more compressed when pressure is applied. On the other hand, the work against turbulence in moving the air is less as the density of the air diminishes.

#### DISCUSSION

The theoretical interpretation of the results which we have obtained in these experiments is best illustrated by means of  $pO_2$ - $pCO_2$  charts. The theory

of these charts has been discussed at some length by Fenn *et al.* (9). Such a chart is shown in figure 6 for the case where pure oxygen is breathed at 42,000 ft. At ambient pressure the alveolar air composition must be represented by a point on the 42,000-ft. diagonal for the equation of this diagonal is  $pO_2 + pCO_2 = B-47 = 81$  mm. Hg. The point N on this diagonal represents the alveolar air breathing oxygen before HV or VPB, the  $pCO_2$  being 33 mm. During hyperventilation without applied pressure the alveolar point moves down the altitude diagonal to H with a  $pCO_2$  of 21 mm. and the arterial saturation increases from 86 to 94 per cent as indicated by the family of curved lines. When VPB is tried at this altitude the alveolar point moves up and to the right in such a way that both  $pCO_2$  and  $pO_2$  increase in proportion to  $(B-47 + p)$  where  $p$  is the mean pressure applied as indicated by the first arrow. At this point the ventilation increases and brings the  $pCO_2$  back to nearly its original value of 32 mm. with a saturation of 94 per cent instead of 86 per cent. The

Fig. 6. DIAGRAM OF CHANGES in alveolar air composition during normal breathing (N), hyperventilation (H) and voluntary pressure breathing (V) at 42,000 ft. breathing oxygen. Ordinates and abscissae are alveolar tensions of  $CO_2$  and  $O_2$  respectively. Diagonal lines represent altitudes and curves are iso-saturation lines. See text.



final position is represented by point V on the diagonal corresponding to an altitude of about 39,400 ft.<sup>4</sup>

A similar chart for 18,000 ft. is shown in figure 7. The alveolar point breathing air at 18,000 ft. before VPB is indicated by point  $N_1$ . As we have shown elsewhere (9) when nitrogen is present in the breathing mixture each altitude is represented not by a single diagonal but by a family of diagonals radiating from the same  $pO_2$  value on the X axis, the slope depending upon the R.Q. Three such diagonals for 0.82, 0.94, and 1.08 are shown for 18,000 ft. and  $N_1$  is located on the diagonal for 0.94. When VPB starts the tensions of both  $O_2$  and  $CO_2$  are increased in the proportion of  $(334 + 19.6)/334$  as indicated by the short line up and to the right from  $N_1$ . This is much less than the corresponding movement at 42,000 ft. because the ambient pressure is so much greater. The increase in ventilation then moves the alveolar point

<sup>4</sup>The reader who is unfamiliar with this chart will find it helpful to note that the position of the alveolar point on a given altitude diagonal depends only on the alveolar ventilation and the metabolic rate. At an infinite ventilation volume or a metabolic rate of zero the alveolar point is still on the same altitude diagonal but at its point of intersection with the X axis where  $pCO_2 = 0$ .

to point V which is on the R.Q. = 1.15 diagonal corresponding to an altitude of about 17,000 ft. In this case the alveolar point does not simply move down one diagonal but the increased R.Q. moves it also to the right to a new diagonal. The point  $N_2$  corresponds to the alveolar air during normal breathing on air after VPB and before HV begins (table 1).  $N_2$  is below  $N_1$  because  $CO_2$  is still being retained; i.e., the subject has not yet recovered from the  $CO_2$  blown off during the VPB. The R.Q. is therefore only 0.82 instead of 0.94. When hyperventilation begins  $CO_2$  is blown off and the R.Q. moves to point H on the 1.08 R.Q. diagonal for 18,000 ft. Comparing points H and V, it is evident that the percentage saturation is a little better at H but both  $pO_2$  and  $pCO_2$  are lower so that the performance is probably not quite so good as at V.

At this point it might be noted that in our 18,000-ft. experiments the effects of HV were compared after VPB when some of the preformed  $CO_2$  had

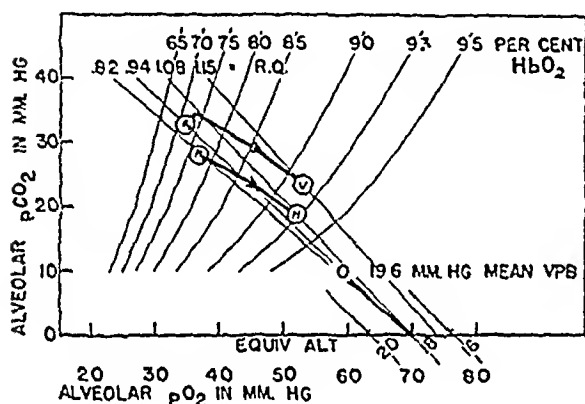


Fig. 7. DIAGRAM OF CHANGES in alveolar air composition during normal breathing ( $N_1$  and  $N_2$ ), hyperventilation (H) and voluntary pressure breathing (V) at 18,000 ft. breathing air. Ordinates and abscissae are alveolar tensions of  $CO_2$  and  $O_2$  respectively. See text.

been blown off and the increase in  $pO_2$  due to this high R.Q. effect was less than normal. The results would presumably have been more favorable to HV if it had been tried before VPB instead of after. Likewise it should be pointed out that because of this R.Q. effect on the  $pO_2$  the simple process of hyperventilation is more useful at 25,000 ft. than at 42,000 ft. When pure oxygen is used there is no such R.Q. effect to assist the subject.

The same  $pO_2$ - $pCO_2$  chart can be used in figure 8 to summarize the situation of a man trying to survive at 25,000 feet with VPB. The normal composition of the alveolar air at a series of increasing altitudes is represented by a broken line which bends down when the  $pO_2$  falls below 50 mm. This bending is due to the hyperventilation which normally occurs with anoxia. If, however, the ventilation were not increased and the R.Q. retained its normal value of 0.8 the alveolar point would be represented by point 1 on the R.Q. = 0.8 diagonal for 25,000 ft. At this point the  $pO_2$  would be only 6 mm. and collapse from anoxia would be inevitable. If at point 1 however the alveolar ventilation were to increase (without change in R.Q.) from a normal value of 7.7 l/min. to 14 l/min. the alveolar point would move down the 0.8 diagonal





vival at 25,000 ft. in case of emergency. A summary of some of the findings is given in table 5. The general conclusion from this table is that both HV and VPB improve the chances for survival at 25,000 ft. On the basis chiefly of their tests under actual flight conditions Houston *et al.* (4) concluded that hyperventilation because of its relative simplicity was better than VPB as an emergency measure. On the whole, neither HV nor VPB permit more than about 50 per cent survival at 25,000 ft. The chief emphasis so far has been upon the application of VPB to survival at 25,000 ft. Actually it is more likely to be useful at altitudes above 40,000 ft. breathing pure oxygen for, under these conditions, all the pulmonary pressure can be applied to the oxygen and the increase in saturation may be considerable.

One of the points stressed by many observers has been the great effort involved in VPB which interferes with the performance of routine tasks and

TABLE 5. PERCENTAGE OF SUBJECTS REMAINING CONSCIOUS AT 25,000 FEET

	NORMAL		VPB		HV	
	%	n	%	n	%	n
Houston <i>et al.</i> (Rep. No. 3)	7	28	88	38	67	38
"    "    " plane			27	31	69	31
Houston <i>et al.</i> (Rep. No. 2)					48	40
Riley <i>et al.</i> , 1944					48	50
This report			43	7	57	14

The figures under *n* indicate the number of subjects involved in the experiments. All experiments were simulated flights in low-pressure chambers except the actual flights in a plane carried out by Houston *et al.* in report No. 3.

fatigues the subject. The 45 per cent increased rate of oxygen consumption which we have measured indicates the magnitude of this effort. It is worth while to consider what this means in terms of diffusion gradients. In the lungs at a diffusion capacity of 60 cc/mm. Hg/min., a 5-mm. gradient is sufficient for a resting rate of oxygen intake of 300 cc/min. If this is increased 45 per cent the gradient will also have to increase by a similar percentage so that a 3-mm. increase would be sufficient. This could easily be expected from a mean pulmonary pressure of 20 mm. if  $\frac{1}{5}$  is applied to the oxygen. Considering the lungs alone an increase of a few mm. Hg pressure might be critical. The diffusion in the tissues must also be considered however. In the alveoli there is an oxygen pressure of 30 mm. of which 5 mm. is used in the lung. The mean  $pO_2$  in the lung capillaries is therefore 25 mm. and the mean pressure in the tissue capillaries could hardly be much greater than 20 mm. If this 20 mm. is barely sufficient to supply the tissues at rest then to take care of a 45 per cent increase in oxygen intake there will have to be also an increase of 45 per cent in the diffusion pressure (or in the tissue diffusing capacity) or 9 mm. more of average oxygen tension in the tissue capillaries. It is hardly

reasonable to expect an increase of this amount in VPB and the increased work involved must be regarded as a definite disadvantage. It is, of course, true that the 45 per cent extra oxygen is used only in the muscles and the important point in an emergency is the maintenance of the oxygen supply of the brain. A few mm. Hg increase in oxygen pressure in the cerebral capillaries for a short time might permit survival until a better oxygen supply is available for the repayment of the oxygen debt incurred, meanwhile, by the muscles.

Our own recommendations for emergency survival would be to breathe a little more than twice as much air as normal; exert a little pressure without excessive effort during expiration if it can be done conveniently. This will be especially useful at oxygen-breathing altitudes. If symptoms of acapnia develop such as tingling in the fingers and toes the amount of breathing should be diminished slightly until this symptom is controlled.

#### SUMMARY

A study was made of the relative effectiveness of a voluntary increase in the pressure of gases in the lung at the height of each inspiration as a means of improving the tolerance to high altitudes in case of emergency. The increase in the saturation of the arterial blood which results from this voluntary breathing pressure breathing (VPB) recommended by Commoner is shown to depend chiefly upon the concomitant hyperventilation. Systematic comparisons were made at simulated altitudes of 18,000, 25,000, and 42,000 ft. of the relative effectiveness of voluntary pressure breathing and simple moderate amounts of hyperventilation. Simultaneous measurements were made of the composition of the alveolar air and the volume of the ventilation.

VPB is more effective at 42,000 ft. breathing oxygen than at 18,000 ft. breathing air because in the former case all of the pressure is applied to the oxygen and in the latter case 80 per cent is applied only to the nitrogen. Hyperventilation on the other hand, is more effective when breathing air because of the increased R.Q. and the resulting nitrogen dilution, or increased oxygen pressure which occurs. Measurements of the rate of oxygen consumption showed an increase of 45 per cent during VPB. This is a measure of the considerable effort required for the development of pressure and greatly diminishes the value of the procedure. Experiments at 25,000 ft. show that an alveolar oxygen tension of 30 mm. is close to the minimal pressure consistent with maintenance of consciousness. Only about 50 per cent of all normal male subjects can maintain consciousness at 25,000 ft. with either voluntary pressure breathing or hyperventilation.

Since hyperventilation is much easier and equally as effective as the arduous voluntary pressure breathing procedure it is recommended for emergency use. The degree of hyperventilation should be a little more than twice the normal and should be diminished if any signs of acapnia appear.

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# *Physiological Observations on Hyperventilation at Altitude with Intermittent Pressure Breathing by the Pneumolator<sup>1</sup>*

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THE PROBLEM of the subject at high altitudes is to regulate the breathing in such a way that the available pressure is divided between oxygen and carbon dioxide in the most advantageous manner. The natural response to this anoxic stimulus is an increase in the ventilation of the lungs and a reduction in the alveolar  $\text{CO}_2$  tension.

In a series of performance tests with varying degrees of hyperventilation we have shown that there is no serious reduction in score until the  $\text{pCO}_2$  in the alveoli is reduced below about 25 mm. Hg (1). In another series of tests carried out at a wide range of oxygen and carbon dioxide tensions we have been able to separate the effects of hypoxia and hypocapnia (2). The results indicate that most of the impairment of performance observed at high altitudes is due to the oxygen deficiency rather than the low  $\text{CO}_2$ . It appeared further that the amount of hyperventilation instinctively resorted to is probably not far from the optimum although in individual cases there may be either too much or too little ventilation over wide ranges. It seemed probable also that the optimum ventilation was different for different functions or types of performance test. In another study of survival at 25,000 feet breathing air (3) we have shown that under these extreme conditions the maintenance of consciousness is prolonged by a volume of ventilation somewhat in excess of that instinctively used by many of our subjects.

In the present paper, we wish to report briefly the results of 22 simulated flights to 46,000 feet using either continuous pressure breathing with natural volume regulation or intermittent pressure breathing with a relative hyperventilation. During these flights we obtained data on the alveolar carbon dioxide tensions as well as figures for the alkaline reserve and lactic acid content of the blood, and the excretion of base in the urine. The apparatus used in these flights for intermittent pressure breathing was the 'pneumolator'<sup>2</sup> the characteristics of which will be described by way of introduction.

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<sup>2</sup> The pneumolator used in these experiments was designed by Mr. J. H. Clough of the General Electric X-Ray Corporation who kindly loaned it to us for this study.

*Characteristics of Breathing on the Pneumolator.* With this apparatus the lungs are inflated to a peak pressure the magnitude of which can be varied by a screw adjustment. When this pressure is reached an expiratory gate is automatically opened which permits the air to leak out until the ambient pressure is restored in the apparatus. The rate of expiration can be varied at will by a second screw adjustment which changes the size of the expiratory orifice. With these two adjustments the volume of ventilation can be varied over a wide range. A sample record of the pressure and the velocity of flow (measured with a pneumotachograph) as a function of time are shown in figure 1. The mean pressures averaged over the whole respiratory cycle were 35 to 45 per cent of the peak pressures, the figure being a little higher at the higher peak pressures.

It is important to note in figure 1 that the velocity of inflow is constant throughout the period of inspiration. This results from the fact that the chief resistance is in the apparatus itself where the pressure drop is from 50 lbs. down to the few inches of water which are necessary to maintain the same flow through the respiratory passages into the lungs. The volume of inflow

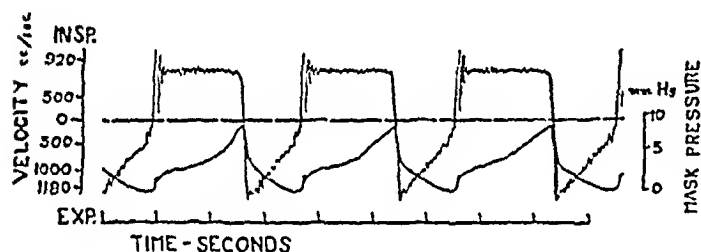


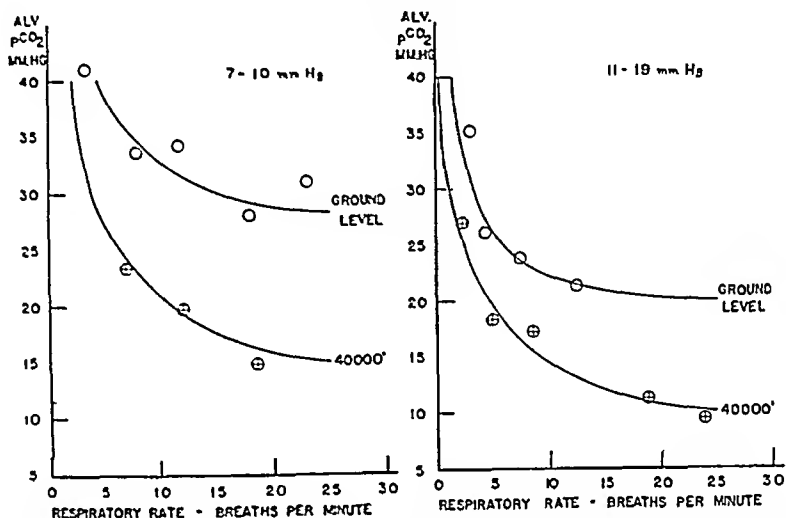
Fig. 1. RECORDS OF MASK PRESSURE and velocity of air flow while breathing on the pneumolator at a peak pressure setting of 5" of water.

and the duration of inflow should both depend only on the elastic capacity of the lungs and chest and the peak pressure setting. The pressure differential between the apparatus and the alveoli should be the same at all frequencies or peak pressures except during the transitional period when inspiration begins and is approaching a steady state of flow.

The minute volume of the ventilation when breathing through the pneumolator is increased above normal to varying degrees. Figures 2 and 3 show the alveolar  $\text{CO}_2$  tension which results at 2 different peak pressures as a function of frequency and altitude. It is evident that doubling the frequency does not reduce the  $\text{pCO}_2$  to half (chiefly because of the dead space). Further the  $\text{pCO}_2$  is always much less at 40,000 ft. than at ground level.

Figure 4 gives a summary of average figures for the alveolar  $\text{CO}_2$  at different altitudes using normal breathing at ambient pressure or pressure breathing of the continuous or intermittent type. The number of figures averaged for each point varies at the different altitudes but was in general between 10 and 100. The result is important in showing 1) that continuous pressure breathing using the standard pressure-demand oxygen regulator neither increases nor decreases the normal ventilation; and 2) that the ventilation is

always greater and the alveolar  $\text{CO}_2$  lower when intermittent pressure breathing is used. All three curves show a decrease in alveolar  $\text{pCO}_2$  as the altitude increases. The figures are not suitable for exact interpretation because they



Figs. 2 (left) and 3 (right). AVERAGE ALVEOLAR  $\text{CO}_2$  TENSION of subjects breathing on the pneumulator at 2 different peak pressure settings as indicated. Approximately 10 figures were averaged for each point. Intermediate curves (not shown) were also obtained at 30,000 and 35,000 feet.

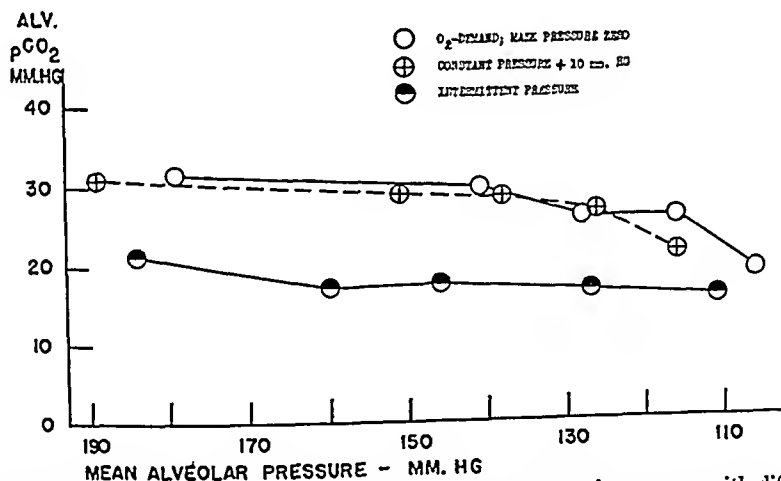


Fig. 4. MEAN VALUES for alveolar  $\text{pCO}_2$  at different barometric pressures with different  $\text{O}_2$  supply systems. Comparison of normal breathing, continuous pressure breathing and intermittent pressure breathing with the pneumulator.

represent many different subjects and many flights and varying durations of stay at each altitude.

The ventilation on the pneumulator is greater at altitude partly because of the diminished resistance to the flow of gases. This

turbulence at low densities. Another reason for the increased ventilation depends upon the low pressure of the gas rather than its low density. Assume that the lung has a volume of  $V$  and does not expand while the pneumolator delivers a tidal volume of  $T$  and causes the pressure to rise from  $P$  to  $P + p$ .

Then  $(V + T) P = (P + p) V$  and  $T = \frac{P}{P + p} V$ . In this equation  $V$  and  $T$

are dry gas volumes in the lung and  $P = B - 47$ , where  $B$  is the ambient pressure. Thus for a given value of  $V$  and  $p$ , the tidal volume is inversely proportional to  $P$ , i.e., it increases with altitude. It is interesting to note also that if  $V = 3000$  cc. and  $P = 81$  mm. (40,000 ft.) a peak pressure of 13.5 mm. will provide a tidal volume,  $T$ , of 500 cc. Under these conditions the pneumolator will adequately ventilate the lungs even if the chest were somehow immobilized. Expansion of the lungs still further increases the ventilation. It is not surprising therefore that the ventilation at high altitudes not only increases when the pneumolator is used but may easily become excessive.

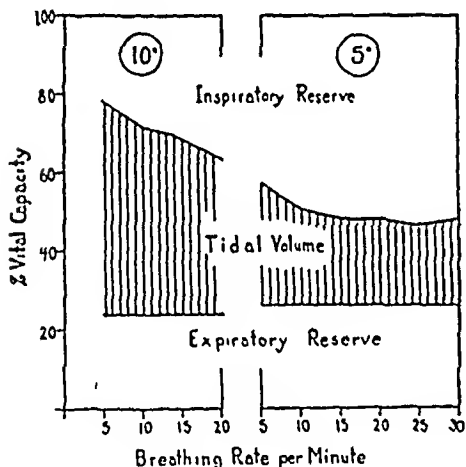


Fig. 5. AVERAGE TIDAL VOLUMES obtained with the pneumolator as a function of breathing rate (abscissae) at two different peak pressures. Shows a decrease in tidal volume caused by acapnia at the higher rates.

Another factor which determines the ventilation obtained with the pneumolator is the distensibility of the chest which varies in turn with the degree of acapnia. This is shown in figure 5 which illustrates the decrease in tidal volume which accompanies an increase in frequency of cycling of the pneumolator at ground level breathing air at two different peak pressures. If the lung and chest behaved entirely passively like a rubber balloon the volume of air needed for inflation to a given pressure would be the same at all frequencies.<sup>3</sup> In the lung however the decrease in  $p\text{CO}_2$  in the alveoli which results from an increase in frequency seems to stiffen the chest reflexly so as to cause a progressive decrease in the tidal volume. The respiratory center is therefore able to control the ventilation to some extent in spite of the pneumolator.

<sup>3</sup> This is true only for an apparatus like the pneumolator in which the velocity of inflow is practically constant under all conditions. Since the rate of air flow through the trachea and the rate of expansion of the chest are constant the pressure gradient from apparatus to lung is independent of the frequency.

In these experiments it was not possible to measure the ventilation merely by passing the inspired gas through a gas meter before it reaches the mask because the pneumolator permits some gas to flow through the intake port even during expiration. At intervals during the experiment, therefore, it was necessary for the subject to turn a large 3-way cock on the mask-intake exactly at the height of inspiration and collect one tidal volume in a small spirometer. While this volume was being measured by the observer the subject held his breath and then proceeded to blow out as much more air as possible, the expiratory reserve, which was again measured in the spirometer. These values are also included in the diagram of figure 5. It can be seen that the lung volume at the end of (tidal) expiration was slightly larger at the lower peak pressure even though ambient pressure prevailed in the lungs at expiration at all peak pressures. If this small difference is real it probably means that the increased reflex resistance to expansion developed at the higher peak pressure during inspiration continued to some extent during expiration.

The data for figure 5 were obtained from over 300 spirometer measurements on 7 different individuals. All the figures are calculated as percentages of the average vital capacity of 4750 cc. The individual variations lie within 10 per cent of the values indicated. All readings were taken after a period of adjustment. Figures for a given frequency were picked by graphical interpolation on a frequency vs. ventilation chart. At each new setting readings were taken every minute or two for 10 or 15 minutes and the results averaged before a new rate was established.

In another study of this same effect the subject lay supine in a Drinker respirator and breathed through a mask connected to a spirometer and a closed-circuit system with absorption of the  $\text{CO}_2$  produced. Measurements were made of the normal ventilation of 8 subjects without using the respirator and again of the passive ventilation produced by the respirator at peak pressures of  $-13$  and  $-25$  cm. of water applied at a frequency of 15 per minute. After a period of adjustment a record of normal breathing was taken for 6 minutes followed immediately by a 15-minute record with the respirator going. Finally a period of recovery was also recorded. The results of these experiments were averaged together and are shown in figure 6. At both pressures the ventilation gradually decreased, the percentage decrease being 39 and 32 per cent for the two pressures as shown in table 1. This again seems to represent a gradual development of some reflex resistance to expansion.

In order to measure the rôle of acapnia in this progressive decrease in ventilation a second series of experiments was tried on 4 subjects in which the loss of  $\text{CO}_2$  was prevented by an increase of 500 to 1000 cc. in the dead space of the rebreathing circuit. This increase in dead space was calculated so as to provide the same alveolar ventilation (and the same alveolar  $\text{pCO}_2$ ) as that obtained in normal breathing. The results of these experiments are shown in figures 7 and 8. The curves show that the ventilation was better maintained when the acapnia was prevented. The decrease in ventilation in



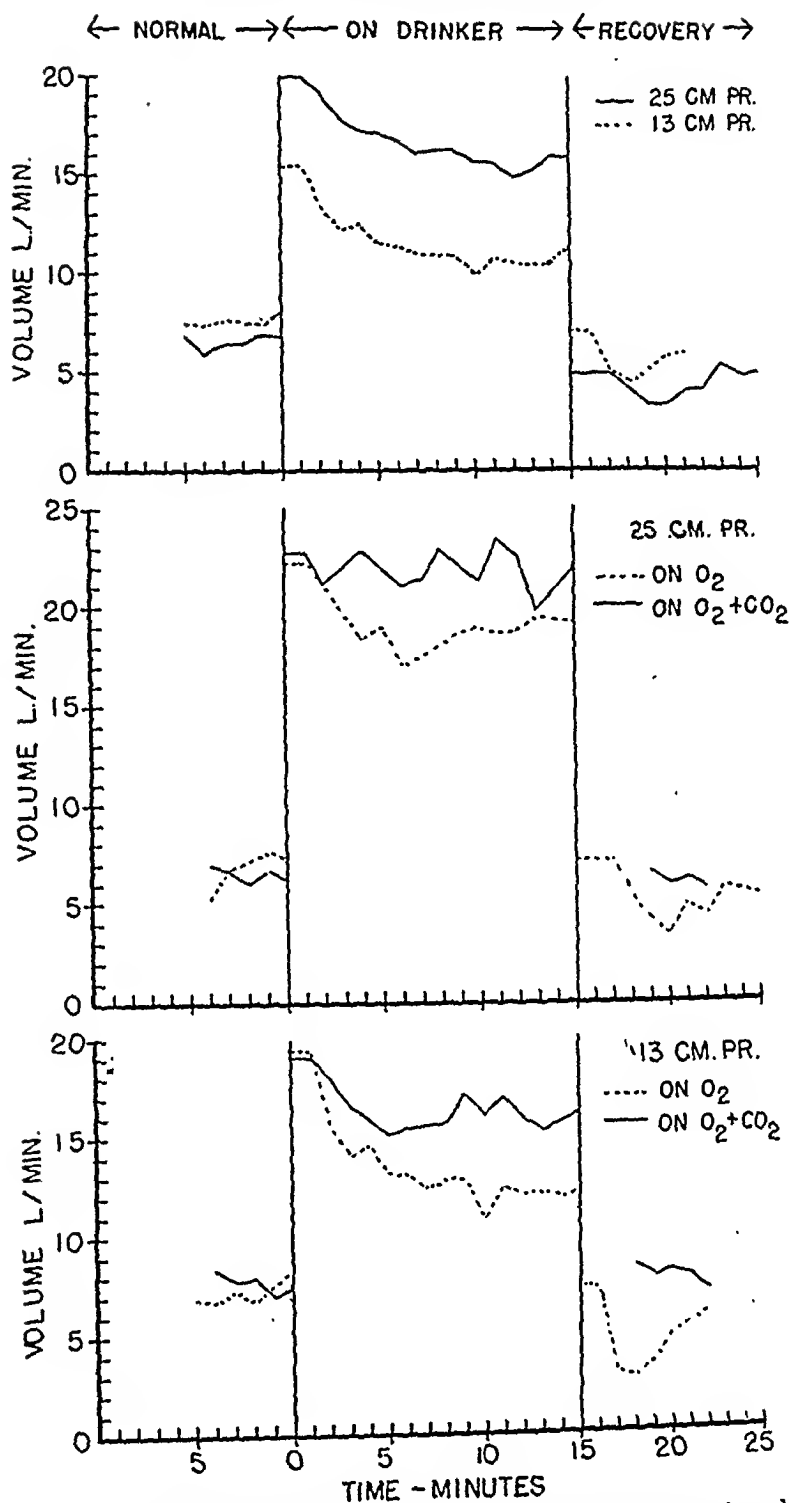


Fig. 6. (upper). AVERAGE MINUTE VOLUME of ventilation in 8 subjects, before, during and after a 15-minute period in the Drinker respirator at 2 different pressures applied intermittently. Abscissae, time in minutes.

Figs. 7 and 8 (middle and lower). AVERAGE VENTILATION of 4 subjects at 2 different pressures as affected by 15 minutes on the Drinker respirator. Solid line represents the same experiment with the addition of a dead space sufficient to prevent the alveolar CO<sub>2</sub> from falling.

per cent of the maximum values is given in table 1. The figures show that most but not all of the decrease may be attributed to the alkalinity of the over-

ventilation. The cause of the remainder is subject for speculation but it cannot be due to failure to prevent a fall in the alveolar  $\text{CO}_2$  tension because alveolar samples were taken at the end of this hyperventilation period which gave approximately normal values of 37.4 and 36.6 mm. in two subjects at 13-cm.  $\text{H}_2\text{O}$  pressure and values of 39.5 and 38.5 for two subjects at 25-cm.  $\text{H}_2\text{O}$  pressure. The alveolar values for hyperventilation without added dead space were not determined directly but were calculated from the alveolar ventilation and the rate of  $\text{CO}_2$  output and were found to be approximately 15 and 23-mm.  $\text{pCO}_2$  for the 13 and 25-cm. pressures respectively.

In these experiments a record was available of every tidal volume and it was of interest to note the variations in the breathing patterns of different individuals. Some breathed with great regularity while others fluctuated

TABLE 1. AVERAGE PERCENTAGE DECREASE IN VENTILATION DURING 15 MIN. OF PASSIVE HYPERVENTILATION ON THE DRINKER RESPIRATOR (WITH STANDARD DEVIATION)

PEAK PRESSURE CM. $\text{H}_2\text{O}$	8 SUBJECTS NORMAL	4 SUBJECTS NORMAL	4 SUBJECTS WITH $\text{CO}_2$
-13	39 $\pm$ 14	47 $\pm$ 13	19 $\pm$ 12
-25	32 $\pm$ 22	23 $\pm$ 18	7 $\pm$ 18

The last two columns refer to the same 4 with and without added  $\text{CO}_2$  (by increase of dead space).

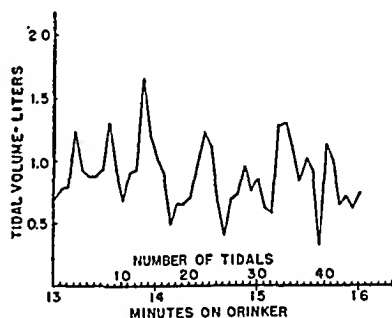


Fig. 9. RHYTHMICAL FLUCTUATIONS in tidal volumes at constant frequency of breathing on the Drinker respirator.

rhythmically over a rather wide range as indicated by the sample record in figure 9.

Theoretically, it should be possible to predict the total volume of ventilation which can be expected for a given peak pressure using the pneumolator or the Drinker respirator if the relaxation pressure curves (4) of the individual are known and the frequency of breathing. We have shown in these experiments however that acapnia in effect changes the position of the relaxation pressure curve or stiffens the chest so that it does not inflate to the expected degree. In 7 of the 8 subjects used in these experiments we have made careful measurements of the volume of the lung in percentage of the vital capacity at the height of inspiration. On the average the theoretical volume at 25-cm.  $\text{H}_2\text{O}$  pressure as calculated from the relaxation pressure curve is 87 per cent of the vital capacity. With continuous pressure breathing at this pressure the actual volume was only 80 per cent. With intermittent pressure breathing at the

same peak pressure of 25 cm. the volumes were 78, 72, 68, and 62 per cent respectively at rates of 5, 10, 15, and 20 breaths per minute. This decrease in inspiratory lung volume is another measure of the increasing resistance to inflation as the acapnia becomes more severe.

In some individuals a change in posture from sitting to supine changes the position of the relaxation pressure curve in such a way that a larger tidal volume would be expected for the same pressure change (25-cm.  $H_2O$ ) in the pneumolator cycle. This was found to be the case in 2 out of 7 individuals the increases in tidal volume being 700 and 900 cc. respectively. This might become important in resuscitation operations.

*Symptoms of Acapnia.* In previous reports (1, 2) we presented the results of performance tests at different degrees of anoxia and acapnia. In general there was no appreciable decrease in score until the  $pCO_2$  fell below 25 mm. so long as adequate oxygen was present. Anoxia combined with acapnia was worse than either alone.

The symptoms of acapnia as we have encountered them using the pneumolator at high altitudes have varied somewhat from one subject to another. If the ventilation rate is suddenly increased at an altitude of 30,000 feet or above, the alveolar carbon dioxide tension falls very rapidly and the subject may suffer an immediate attack of dizziness. If this dizziness is of such an intensity that it can be tolerated for a short time, it disappears. If the acapnia comes on more slowly, the dizziness may not appear at all and the first symptom will then be a tingling in the fingers or the toes. This tingling may become progressively worse until it extends up the legs to the waist or beyond. After this tingling continues for some time it also may disappear altogether in some subjects even though the alveolar  $pCO_2$  continues to fall slightly. Thereafter the only symptoms of acapnia may be a slight tremor or unsteadiness or a deficient mental performance. In this stage the occlusion of the blood flow to the arm by a pneumatic cuff may bring on a spasm of the muscles of the arm. Along with the tingling there may be cold sensations in the legs and thighs or a feeling of tightness as if the tone of muscles was increased or as if the muscles were about to go into tetany. Some individuals experience tingling in the chest or face and one of our subjects becomes unable to talk intelligibly because of spasms of the facial muscles. Another of our subjects (H.R.) on two occasions has practically become unconscious from acapnia, failing to respond to signals and making glaring errors in his manipulations. He does not actually faint but simply sits upright, apparently normal but quite unresponsive. He has twice reacted, however, in exactly the same way at 50,000 feet while breathing from the pressure-demand system, an effect presumably due in this case to anoxia.

Tremor of the hands is a common symptom of acapnia which is clearly evident in the handwriting and is measured by the hand steadiness test previously described. In one subject, sleepiness and listlessness were the only

symptoms which we could elicit and these occurred in many subjects to varying degrees.

*Simulated Flights to 46,000 Feet.* In our small two-man chamber we have carried out 22 flights to this altitude one subject using the pneumolator and the other using the standard continuous pressure-demand system. Alveolar  $p\text{CO}_2$  has been followed carefully in all cases.<sup>4</sup> Seven different subjects have reached the 46,000-ft. altitude and with one exception all have continued for one hour. One subject collapsed within about 10 minutes on 3 different trials. This was probably attributable to the effects of pressure on the circulation because the same subject collapsed at ground level from pressure alone 3 times and has tolerated considerably lower oxygen tensions without PB at 25,000 feet breathing air. In one flight both subjects reached 50,000 feet and remained conscious for 10 minutes but in two other flights attempts to repeat this performance necessitated emergency descents. Some performance tests were tried on these flights as a measure of the condition of the subject and these have been included in part in a previous report. Regardless of any such tests however it was clear both to the observers and the subjects that the man using the continuous pressure breathing was in a better condition and would be safer as the pilot of a plane than the more acapnic individual using the intermittent pressure breathing system. The results might have been different however, if the pneumolator had been so adjusted as to prevent the alveolar  $\text{CO}_2$  tension from falling below 25 mm. This result must not be taken to indicate therefore that all continuous PB is better than intermittent PB. The result will depend upon the particular settings and the particular apparatus used. In the Bennett valve for intermittent PB, for example, the pressure is allowed to fall only part way toward zero during expiration so that the mean pressure is considerably greater for the same peak pressure and the tendency to overventilation is less than that found on the pneumolator. This would probably be superior to continuous PB.

In our original report (5) all the experiments which we have done both at 46,000 feet and at other altitudes including those at 18,000 to 25,000 feet breathing air have been plotted in 8 separate charts like that in figure 10, one chart for each of our subjects. Solid symbols indicate that there were symptoms of acapnia or anoxia recorded while hollow symbols indicate that the

<sup>4</sup> Most of the alveolar  $\text{CO}_2$  values recorded in these flights were obtained from samples drawn by a syringe from the expiratory tube of the mask after a forcible expiration. These were analyzed at once by the Scholander method in which a known volume of gas (about 10 ml.) is delivered by the syringe directly through a rubber tube into a vessel containing KOH, the unabsorbed volume being measured at ambient pressure in a 10 ml. graduated stem sealed to the vessel. In carrying out this analysis we found that the reliability of the results could be much improved if during the analysis the observer regulated the pressure in the chamber with extreme care by reference to a water manometer located inside the chamber. One end of this manometer terminated in an air reservoir which was cut off from communication to the chamber by a clip applied by the subject inside the chamber when the analysis was about to begin. With this arrangement the Scholander analyses were very uniform but for some unknown reason averaged 2 mm. below values obtained by analysis of samples taken over mercury and analyzed after descent on a Haldane apparatus.

subject appeared to be in good condition. Each diagonal line extending from the top to the bottom of the chart indicates a given altitude or ambient pressure (breathing pure oxygen) and the short slanting lines extending from some of the symbols down and to the left to an altitude diagonal indicate the increase in  $\text{CO}_2$  and  $\text{O}_2$  pressure which was obtained by pressure breathing. It can be seen that this increase from intermittent PB (small circles) was much less than the gain from continuous PB (large circles) because the mean pressure was less. In this particular subject there seemed to be no symptoms at alveolar  $\text{CO}_2$  levels above 20 mm. and this was typical of most of our subjects (except A.B.O. who showed symptoms at 25 mm.). One of our subjects had a tendency to hypoventilate at 46,000 feet and felt better when he was urged to

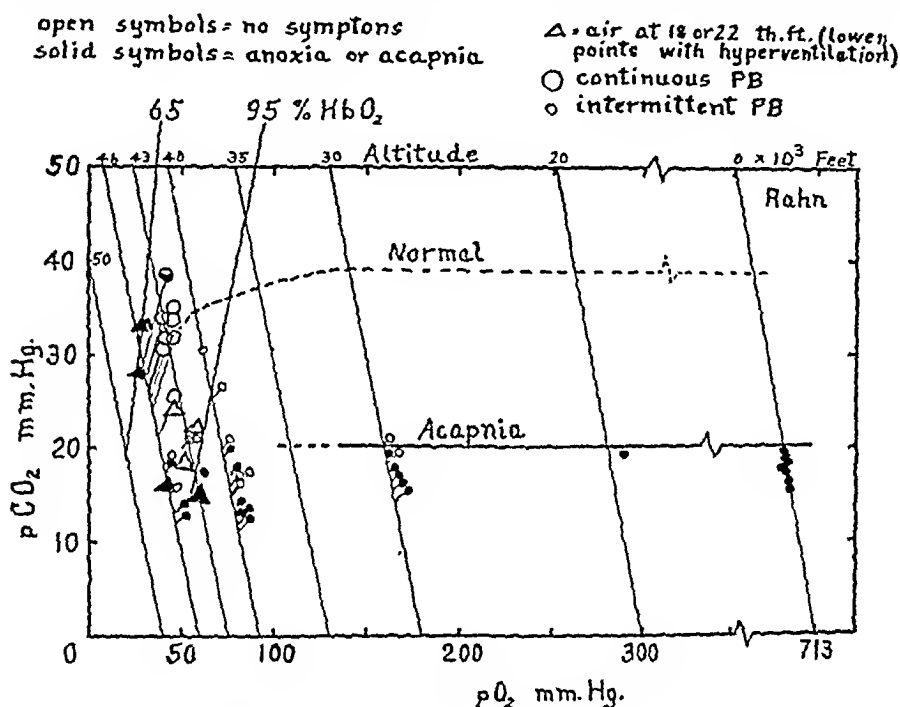


Fig. 10. RECORD ALVEOLAR  $\text{PCO}_2$  AND  $\text{PO}_2$  on many flights by subject Rahn.

breathe more deeply. This shows again the supreme importance of obtaining an optimum breathing volume at altitude.

The dotted line in figure 10 for normal alveolar air was drawn in accordance with average results obtained in breathing without PB at different altitudes. Averaging 16 to 21 different flights the alveolar  $\text{pCO}_2$  values at 30, 40, and 42 thousand feet were 39.0, 34.8, and 32.0 mm. Hg, respectively.

Finger temperatures were measured during these and similar flights to other altitudes. For this purpose the subject merely grasped between his thumb and finger a series of copper constantan junctions which recorded on a galvanometer outside the chamber. The results were somewhat variable due to the differing conditions of the subjects. In the subjects who were using the pneumolator the temperature fell in about half the cases. Anoxia alone ap-

parently had some tendency to cause cooling because a drop in finger temperature was observed in a third of the subjects using continuous PB at 46,000 feet and in half the subjects breathing air without PB at 18,000 feet. None of the subjects at 30,000 ft. breathing oxygen from the demand regulator (without pressure or anoxia) showed any fall in temperature. These results include some measurements made of toe temperatures by a thermocouple continuously in contact.

An attempt was made to confirm this suggestive evidence of vasoconstriction during hyperventilation by measurements of leg volume while hyperventilating with the pneumolator at ground level. The results were conflicting because of inadequately standardized conditions. In general it might be said that out of 10 experiments 5 showed a decrease in volume, 1 an increase and the rest showed no definite effect either way. A decreased blood flow through the hands during hyperventilation has been reported by Stewart (6) and by Schneider (7).

*Chemical Compensations in Hyperventilation.* Numerous studies of the effect of hyperventilation on the blood and urine have been recorded in the literature.

Increased alkalinity of the urine, suppression of ammonia excretion, and production of acetone bodies in the urine are known to occur (8-10). Peters *et al.* (11) observed an increase in the organic acid of the blood but found no change in the carbon dioxide capacity. Bock, Dill, and Edwards (12) reported an increase in blood lactate but found no appreciable change in the alkaline reserve. Davies, Haldane and Kennaway (10) also found that the carbon dioxide dissociation curve remains unaltered. Grant and Goldman (8) reported large decreases in the carbon dioxide capacity of plasma, but their measurements were made on plasma separated at the carbon dioxide tension existing when the blood was drawn and so indicate nothing as to any real change in the whole blood. Shock and Hastings (13) found an increase in the fixed acid of the blood if the overventilation persisted long enough. Gollwitzer-Meier (14) and Rapoport *et al.* (15) report an increase in chloride, a decrease in sodium and a rise or no change in potassium.

All the above experiments were carried out on subjects voluntarily hyperventilating, and, in most cases, for relatively short periods of time. Consequently, it seemed desirable for the study of survival at altitude to secure some measurements on subjects hyperventilating passively for an hour or more with the aid of the pneumolator. If such hyperventilation is performed at altitudes of 30,000 feet or above, it can be carried on with ease for long periods. At ground level, the greater resistance of the air (due to turbulence) is such that it is difficult to lower the  $p\text{CO}_2$  to the point of evident acapnia in most subjects. The greater resistance occurs presumably at the oxygen inflow orifice in the pneumolator so that it is necessary for the subject to 'lead the machine' very much and produce large negative pressures on inspiration in order to obtain the necessary volume of ventilation.

The flights described above in which subjects remained for one hour or

more at simulated altitudes of 30,000 and 45,000 feet provided an opportunity of obtaining the data desired.

### METHODS

Blood and urine samples were collected from the subjects just before they entered the chamber for a flight. The time of the latest previous urination was recorded. Samples were again collected when the subject emerged from the chamber following the flight. The blood samples were obtained from the cubital vein and placed in a flask containing 35 mg. of sodium fluoride per 10 ml. of blood. When it was not possible to begin the analyses immediately, the blood was stored in an ice bath.

Lactic acid was determined by the method of Barker and Summerson (1941). The carbon dioxide combining capacity was obtained by equilibrating the blood with a mixture of 4.8 per cent  $\text{CO}_2$  and 95.2 per cent  $\text{O}_2$  in tonometers at  $38^\circ \text{C}$ . and analyzing the equilibrated blood for  $\text{CO}_2$  by the method of Van Slyke and Neill (1924).

The volume of each urine sample was noted and the  $\text{pH}$  was measured with a Beckman  $\text{pH}$  meter. As a measure of base excretion, an aliquot was titrated to  $\text{pH}$  7.4 by addition of 0.1 N HCl or 0.1 N NaOH as required. The reading of the glass electrode was used to indicate the end point.

### RESULTS

Results of the analyses are shown in table 2. For purposes of comparison the flights have been divided into four groups as follows: 1) flights at 30,000 ft. with the subject breathing oxygen from a demand system; 2) flights at 30,000 ft. with the subject breathing oxygen from the pneumolator; 3) flights at 46,000 ft. with the subject breathing oxygen from the Pioneer Pressure-Demand System (continuous P.B.); and 4) flights at 46,000 ft. with the subject breathing from the pneumolator.

In groups 1 and 3 there was hyperventilation present only to the extent that it spontaneously occurred due to altitude, whereas in groups 2 and 4 additional hyperventilation was imposed on the subject by the pneumolator. In groups 1 and 2 there was no hypoxia. In groups 3 and 4 varying degrees of hypoxia were present.

The results shown in detail in table 2 are summarized in table 3. The figures show that, on the average, with the pneumolator at either 30,000 or 46,000 feet there was an increase in lactic acid concentration, a decrease in bicarbonate  $\text{CO}_2$  capacity and an increase in the rate of excretion of base in the urine. The increase in lactic acid concentration is presumably the direct result of an increase in the alkalinity of the blood caused by hyperventilation (12, 16, 17). When lactic acid is added to normal blood at constant carbon dioxide tension about  $\frac{2}{3}$  of it is neutralized by loss of bicarbonate while the remainder is combined with base taken from the buffers of the blood. Since

at 30,000 feet on the pneumolator the addition of 1.5 mEq. of lactic acid to a liter of blood caused an average decrease of 1.0 mEq. of bicarbonate per liter of

TABLE 2. CHEMICAL CHANGES DUE TO HYPERVENTILATION IN SIMULATED FLIGHTS TO HIGH ALTITUDES

	SUB- JECT	FLIGHT NO.	BLOOD LACTATE		CO <sub>2</sub> CAPACITY		pH OF URINE		ACID EXCRETION		URINE FLOW		ALVEOLAR pCO <sub>2</sub>	OXI- METER
			Before	After	Before	After	Before	After	Before	After <sup>1</sup>	Before	After		
			mEq/l.	mEq/l.			mEq/hr.	m/hr.	mm. Hg	% sat.				
30,000 ft., O <sub>2</sub> demand	HR	137	0.5	1.1			6.42	7.65	0.3	-0.2	29	47	36	Oximeters were not used on the 30,000 foot flights.
	VS	142	1.8	1.4	19.2	18.4	5.50	5.52	0.9	1.1	18	34	33	
	VS	145	2.1	1.8	19.1	20.1	4.90	5.10	0.8	0.7	16	41	33	
	CB	146	1.3	2.0	20.5	19.5	5.77	6.10	0.7	1.0	30	38	34	
	Means.....		1.5	1.6	19.6	19.3	5.65	6.09	0.7	0.7	23	40	34	
30,000 ft., GE pneumulator	WF	125	2.4	3.9			5.91	7.05	0.9	0.1	45	47	15	
	HR	134	0.5	1.1	20.0	18.2	5.90	7.05	0.6	-1.2	27	70	18	
	CB	137	2.0	3.3	18.3	17.5	7.40	7.50	0.0	-0.1	72	99	19	
	HR	142	1.3	4.0	19.4	18.0	6.84	7.90	0.2	-0.4	37	49	22	
	RG	145	1.9	3.8	19.1	18.3	6.40	7.40	0.7	-0.8	177	132	20	
	JF	146	1.8	2.9	19.9	18.7	5.25	6.95	2.1	-0.2	36	60	21	
	WF	147	2.9	2.5	17.7	17.9	6.10	7.43	0.6	-0.2	40	69	17	
	RG	148	1.7	3.5	20.5	19.0	6.80	8.10	0.5	-0.6	24	58	24	
	CB	154	2.5	5.8	19.5	18.7	6.16	7.70	0.8	-0.7	59	46	16	
	Means.....		1.9	3.4	19.3	18.3	6.31	7.58	0.6	-0.5	57	70	19	
46,000 ft., PB demand	ME	138	1.9	1.7	18.5	19.1	5.55	5.95	4.5	0.9	103	36	34	65-70
	LC	139	2.0	1.3	17.8	18.1	5.30	6.68	1.7	-0.9	49	68	27	78-85
	AO	143	2.2	1.6	18.0	19.3	6.64	7.20	0.3	-0.1	58	54	30	60-80
	AO	144	2.9	1.4	19.2	19.6	6.45	6.95	0.4	-0.1	44	45	27	60-80
	HR	149	1.7	1.3	20.4	18.9	5.95	5.40	0.7	2.6	26	55	34	60-70
	ME	152	1.6	2.2	20.1	18.0	6.59	6.97	0.4	0.2	39	52	36	75-86
	HR	156	1.8	1.7	20.2	19.8	5.92	7.61	0.5	-0.3	44	46	28	65-75
	Means.....		2.0	1.6	19.2	19.0	6.06	6.73	1.2	0.3	52	51	31	
46,000 ft., GE pneumulator	JF	131	1.5	4.0	19.8	17.4	5.71	6.65	1.2	0.6	49	99	15	95
	CB	133	0.7	1.2	18.4	17.8	6.20	7.55	0.7	-0.6	48	75	19	80-92
	CB	135	1.5	1.6	18.5	16.7	6.12	8.10	0.7	-0.7	45	55	17	85-95
	AO	136	1.7	2.2	19.4	17.8	5.56	7.28	0.1	0.1	31	183	20	91-94
	JF	138	1.0	5.4	20.0	17.2	5.10	7.25	3.1	-0.6	99	143	16	93-95
	WF	139	2.2	2.5	17.8	15.9	5.80	7.40	0.6	-0.2	31	100	17	87-93
	HR	143	1.9	1.4	19.7	18.8	5.51	8.30	1.1	-1.1	35	54	21	85-95
	HR	144	1.5	4.0	19.8	18.8	5.45	7.61	1.0	-0.4	32	53	16	95-97
	ME	149	2.0	1.6	19.6	17.8	5.80	8.09	1.4	-0.1	34	46	18	89-97
	AO	152	1.8	3.0	19.7	18.6							19	85-93
	ME	156	2.2	3.8	20.5	17.8	6.25	7.61	0.7	-0.4	42	97	24	90-93
	JF	157	2.1	2.7	20.5	19.9	5.15	6.91	2.7	-0.2	57	110	28	90-94
	AO	160	1.8	3.0	20.0	18.6	5.79	7.40	0.4	-0.3	62	310	20	80-93
	Means.....		1.7	2.8	19.5	17.9	5.70	7.51	1.1	-0.3	47	110	19	

<sup>1</sup> Since the column headed 'Acid Excretion, After' does not always appear to be consistent with 'pH of Urine, After', a word of explanation is necessary. The values for acid excretion are corrected for the time between 'before' and 'after' samples not spent at altitude. During this time which averaged 26 minutes, it was assumed that the rate of acid excretion was that indicated by the 'before' sample.

blood, it may be concluded that at this altitude the lactic acid is responsible for all of the change in the CO<sub>2</sub> dissociation curve of the blood. At 46,000 feet, however, the change in lactic acid concentration (+1.1 mEq/l.) accounts



for only about half of the bicarbonate change ( $-1.6$  mEq/l.). Calculation shows that the increased excretion of base in the urine is too small to account for more than a small fraction of the remaining change in the bicarbonate so the presence of some other acid in the blood is to be suspected. A decrease in the excretion of ammonia might be another contributing factor as well as the decrease in sodium and increase in chloride reported by Gollwitzer-Meier (14) and by Rapoport *et al.* (15).

The exact mechanism by which the undesirable effects of excessive hyperventilation (numbness, tingling, tetany etc.) are produced is unknown, but it would seem that the fundamental disturbance is an increased alkalinity of the blood and tissues. It is of interest, therefore, to estimate the magnitude of the compensation that will be produced by the slight lowering of the  $\text{CO}_2$  capacity found in our experiments.

TABLE 3. ACID-BASE CHANGES DURING HYPERVENTILATION AT ALTITUDES

$\text{pCO}_2$	% SATURATION	ALTITUDE	CHANGE IN $\text{CO}_2$ CAP.	CHANGE IN LACTIC ACID	CHANGE IN EXCRETION OF BASE	CHANGE IN URINE FLOW	GROUP NO.
			mEq/l.	mEq/l.	mEq/hr.	ml/hr.	
37	96	30,000 ft. O <sub>2</sub> demand	-0.3	+0.1	0.0	+17	1
20	96	30,000 ft. Pneumolator	-1.0	+1.5	+1.1	+13	2
35	70	46,000 ft. P.B. demand	-0.2	-0.4	+0.9	-1	3
20	85	46,000 ft. Pneumolator	-1.6	+1.1	+1.4	+63	4

By the methods described in the *Syllabus of Methods from the Harvard Fatigue Laboratory*, approximate  $\text{CO}_2$  dissociation curves have been constructed for our average pre-flight blood and for blood after hyperventilation at 46,000 feet. From these curves one can estimate that at a  $\text{pCO}_2$  of 19 the original blood will have a  $\text{pH}$  of 7.63, while the blood after hyperventilation will have a  $\text{pH}$  of 7.60. Or, stated in a different fashion, the blood after hyperventilation will have the same  $\text{pH}$  at a  $\text{pCO}_2$  of 19 as the original blood would have at a  $\text{pCO}_2$  of 21. This is a very small compensation and falls far short of keeping the  $\text{pH}$  in normal limits.

The  $\text{pH}$  of our pre-flight blood at a  $\text{pCO}_2$  of 40 is estimated to be 7.4. If the blood were to have the same  $\text{pH}$  at a  $\text{pCO}_2$  of 19 the carbon dioxide capacity would have to drop by about 7.2 mEq/l. To accomplish this by production of lactic acid would mean increasing the lactate concentration of the blood by about 11.2 mEq/l. This is 3 times the greatest increase we have observed in our subjects and 8 to 9 times the average increase. The formation of lactic acid which we have observed represents therefore a 10 to 20 per cent

compensation for the alkalinity of hyperventilation. This figure, however, is based upon blood samples taken immediately after the flight and it is possible that the lactic acid disappears rather quickly after the ventilation returns to normal. To lower the carbon dioxide capacity of the blood by 7.2 mEq/l. by excretion of increased amounts of base in the urine would require excretion of 36 mEq/5 l.  $\times$  7.2 mEq/l.) of base from the blood plus perhaps 5 times this amount from the tissues or a total of 180 mEq. At the rate of 1.4 mEq./hr. observed in our subjects at 46,000 feet this would require about  $5\frac{1}{2}$  days.

It should be noted that the chemical changes reported above refer to differences between two blood samples taken immediately before and immediately after the flight. The small size of our chamber made it inconvenient to take blood samples during the actual flight and it was felt also that this might interfere with some of the other measurements which we were making. In order to confirm some of the findings we carried out 5 experiments on hyperventilation at ground level. This was found much more difficult than at altitude on account of the greater resistance to air movement and it was necessary for the subject to make considerable efforts in order to keep the alveolar CO<sub>2</sub> tension in the neighborhood of 20 mm. for long periods of one hour. Three subjects reached 20 mm., one reached 25 mm. and one 30 mm. In the 4 who reached 25 mm. or below there was an increase in the lactic acid concentration of the blood of 0.5 to 1.5 mEq/l. which is in good agreement with figures of Bock *et al.* (12). In the other subject there was a slight decrease in lactic acid.

The changes in plasma potassium were scarcely significant although in three cases there was a slight fall, (av. 0.4 mEq/l.), in one case no change, and in one case where the hyperventilation was least, a rise. Rapoport *et al.* (15) reported a slight rise of 0.3 mEq/l. in 2-6 minutes of hyperventilation. Our hyperventilation lasted much longer but the changes were of the same order of magnitude although usually opposite in direction. On the whole it is difficult not to support the conclusion of Gollwitzer-Meier (14) that there is no significant change in plasma potassium under these conditions.

#### DISCUSSION

At an altitude of 46,000 feet the aviator has the problem of breathing deeply enough to avoid anoxia without breathing so deeply as to suffer the disadvantages of acapnia. Of the two dangers anoxia is the more insidious because it gives less warning and the threshold is sharper. Acapnia is a more gradual type of incapacitation and if it comes on slowly a very low carbon dioxide tension may be tolerated without serious consequences.

In subjective symptoms we have found that acapnia and anoxia are synergistic. This may not be true of all performance tests and it is not true of cerebral flow for the vessels dilate with anoxia and constrict with acapnia (18).

Hill and Flack (19) reported that the symptoms of acapnia resulting from ground-level hyperventilation could be prevented by the inhalation of oxygen. We have been unable to confirm this observation in a number of experiments carried out for this purpose. We also tried hyperventilation at ground level on air and on 9 per cent oxygen in nitrogen and seemed to find an earlier rather than a later onset of acapnia in the low oxygen mixture. As a more acute test we took one subject to 18,000 feet where he hyperventilated on the pneumolator breathing air. After signs of acapnia had appeared he changed abruptly to pure oxygen without changing the rate or depth of his breathing and experienced no perceptible change or alleviation in his symptoms. After another 15 minutes he changed back to air and failed again to notice any change in his condition. While these tests are not conclusive by themselves they do not encourage the idea that acapnia and anoxia are antagonistic in their effects on performance as they seem to be on the cerebral blood flow.

#### SUMMARY

Intermittent pressure breathing on the pneumolator results in hyperventilation and a lowering of the alveolar  $\text{CO}_2$  tension. This hyperventilation is greater at altitude than at ground level because of the decreased resistance to air flow and because a larger tidal volume is necessary to produce the same peak pressure at the lower ambient pressure. The expansion of the chest during inflation with the pneumolator is not entirely passive. As acapnia develops the chest seems to expand less for the same pulmonary pressure. This is shown also by measurements of passive ventilation on the Drinker Respirator.

Simulated flights to 46,000 feet are described in which comparisons were made between continuous pressure breathing and intermittent pressure breathing. It was found that the higher oxygen tension and arterial saturation which resulted from the greater ventilation obtained on the latter system were not sufficiently advantageous to compensate for the lower mean pressure in the lungs so that under the conditions of these experiments the subjects preferred continuous to intermittent P.B. There is however a possibility that an intermediate system might be better than either. During these one hour periods of hyperventilation at high altitudes the alveolar  $\text{CO}_2$  tension fell to 20 mm., the alkaline reserve of the blood fell 1.3 mEq/l. and the lactic acid concentration of the blood rose an approximately equivalent amount. The  $\text{pH}$  of the urine and the excretion of base also increased but the absolute amount of base lost in this way was not sufficient to have a significant effect on the alkaline reserve of the blood.

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# *Muscle Action Potentials in Human Poliomyelitis Before and After Closed Manual Neurotripsy<sup>1</sup>*

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**B**ILLIG, VAN HARREVALD AND WIERSMA(1) have reported that the muscle power of patients with anterior poliomyelitis may be improved by techniques designed to cause the intact nerve fibers supplying partially paralyzed muscles to branch profusely and thus presumably innervate larger numbers of muscle fibers than before such treatment. This is shown schematically in figure 1. Because of the importance of these findings for the treatment of poliomyelitis, the Philadelphia Chapter of the National Foundation for Infantile Paralysis suggested a validation test of this relatively new procedure. Toward this end it was proposed: 1) that the muscle power of patients treated by Billig's method of 'closed manual neurotripsy' be tested by a group of physicians and physical therapists different from the team doing the operations; 2) that an electromyographic study be made in an attempt to obtain an objective measure of the value of the method employed; and 3) that results of the muscle testing by the usual clinical method and the electromyographic data be kept separately until the termination of the experiments.

This paper deals with the findings obtained by electrical measurements. Results of manual muscle testing will be reported elsewhere.

## DESCRIPTION OF PATIENTS

Twenty patients, 11 female and 9 male, who had shown no change in muscle power for at least one year despite the usual courses in physical therapy, muscle training etc., were selected for study. The group examined included individuals from 6 to 23 years old, 18 of whom were under 18 years of age. The first signs of anterior poliomyelitis were recognized 1.8 to 13.7 years previous to the first electrical examination. Duration of the disease at the time of initial electromyographic test was from 22 to 26 months in 4 patients, and exceeded 52 months in the remainder of the series.

## METHODS

The details of the method for obtaining muscle action potentials have been reported by Hodes, Larrabee and German(2). The main points of

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the technique are as follows: the nerves supplying the musculature of the forearm, hand, leg and foot are stimulated percutaneously by brief condenser discharges of sufficient intensity to excite all the skeleto-motor nerve fibers in the trunk. The maximal muscle action potentials thus evoked are led from surface electrodes, amplified by a condenser-coupled differential amplifier and photographed on continuously moving bromide paper from a 5-inch cathode-ray oscilloscope.

The plan of the experiments was to obtain one or more muscle action potentials before 'closed manual neurotripsy'<sup>2</sup> was instituted, and to compare with these control values the magnitude of the electromyograms elicited

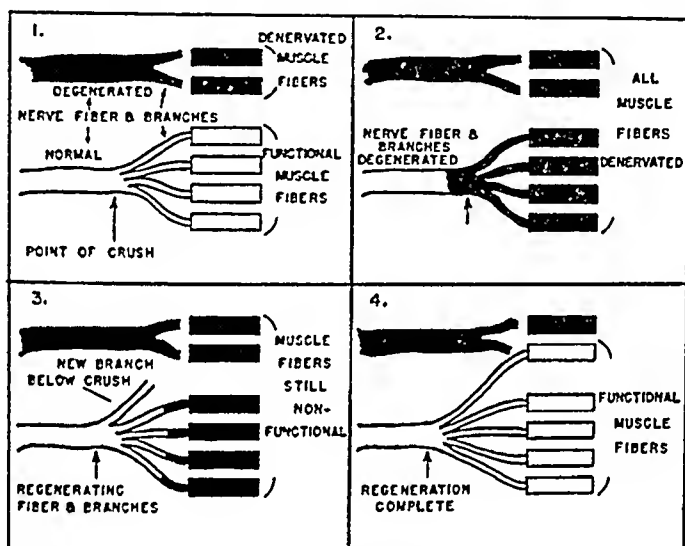


Fig. 1. SCHEMATIC REPRESENTATION of peripheral neuromuscular changes resulting from neurotripsy. Functional axon is crushed (arrow) near its entrance into muscle (1), at first degenerates, (2), later begins regeneration and sprouting peripheral to crush (3), and finally re-innervates more than the original number of muscle fibers (4). No improvement of function would be expected if *entire* nerve supply of muscle were previously destroyed by poliomyelitis (see RESULTS and DISCUSSION).

at various times (0.9 to 17.8 months) after operation. Since the evaluation of the efficacy of the operative procedure depended upon the comparison of post-operative with control action potentials, it was of importance to know the degree to which the electromyograms of untreated muscles varied over a period of time comparable with the time of study of the treated muscles. For this reason 74 duplicate and triplicate determinations, 0.9 to 17.8 months apart, were made of 27 muscle groups of 11 patients. For reasons which will become apparent later the duplicate controls were taken from those patients in whom only the opposite extremity had been subjected to neuro-

<sup>2</sup> Operations were performed at the St. Luke's Hospital, Philadelphia, by Dr. Donald Jones, with the assistance of Mr. Joseph Bruno, physical therapist. The cooperation of the Board of Directors of St. Luke's Hospital in making the facilities of the Hospital available is gratefully acknowledged.

tripsy. A description of the calculations involved indicates the way in which variations in control action potentials are presented. The maximal action potential obtained from the posterior muscles of the leg supplied by the tibial nerve has a mean value of 15.5 mV. in normal muscles (3). On the first control examination a maximal electromyogram of 9.1 mV. was obtained from these muscles of *patient A. A.* The control percentage of normal potential is thus  $9.1/15.5$ , or 59 per cent. Thirteen months later these muscles (which were not treated) were tested again and gave an action potential which was 11.3 mV. or 73 per cent of normal. The percentage of normal action potential of the second control was thus 14 per cent greater than the percentage of normal potential of the first control. The greatest individual difference between the initial control and any subsequent control value was 50 per cent, and the average difference was 4.0 per cent. When a frequency distribution of the differences between the second or third and the first control is made

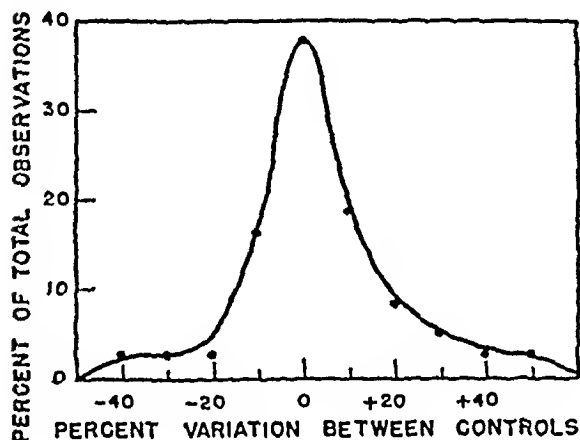


Fig. 2. VARIABILITY OF CONTROL ELECTROMYOGRAMS obtained in 74 tests of 27 untreated muscles of 11 patients, 0.9 to 17.8 months after 1st control measurement. The abscissa represents the percentage difference between the 2nd or 3rd control action potential and that of the 1st control. The difference is expressed as 'change in percentage of normal potential,' as described in the text.

(fig. 2) it is clear that most (73 per cent) of the variations are within  $\pm 10$  per cent of the first control and the most likely difference is zero. Such a distribution strongly suggests that the variability in the controls is due to unsystematic fluctuations in either the techniques employed or in unknown factors inherent in the muscles studied. These random variations in control values stand in marked contrast to the systematic changes which will now be described for the treated muscles.

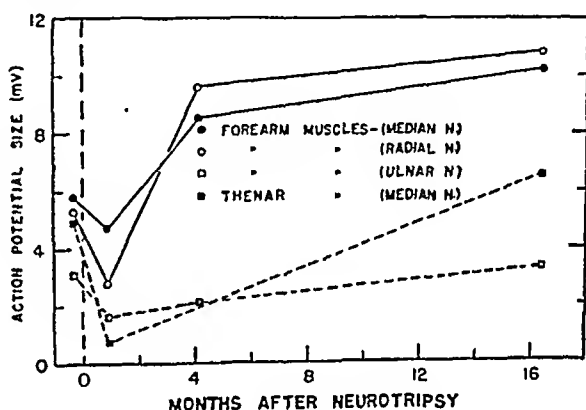
## RESULTS

*Muscles Yielding no Action Potentials on Nerve Stimulation.* In 29 muscles of 10 patients no action potentials were obtained even though intense stimuli were applied to the skin in regions where experience had indicated that considerably weaker stimulation would readily evoke maximal electromyograms by excitation of the normal or partially depleted nerve trunk. *Action potentials were never obtained from any of these muscles on repeated testing from 4.1 to 17.8 months after neurotripsy.*

The difference between these results and those of Billig, Van Harrevald and Wiersma(1) will be taken up later in the DISCUSSION.

*Partially Denervated Muscles.* Some of the changes that are observed after neurotomy in muscles which still retain a portion of their skeleto-motor innervation may be seen in figure 3. In this graph the maximal action potentials obtained from several muscle groups of the upper extremity of one patient are plotted as a function of time after operation, the values to the left of zero time representing the control electromyograms. It is apparent from figure 3 that all the potentials obtained at 0.9 month after neurotomy are less than their respective controls. Since it has been shown in poliomyelitis that electromyogram amplitude and muscle strength are related (3), this finding indicates that a loss of muscle power has resulted. By 4.1 months 2 of the potentials are well above the controls and a third value shows some recovery from the deficit of motor function observed at 0.9 month. By

Fig. 3. CHANGES IN AMPLITUDE of electromyograms of muscles of upper extremity of 1 patient at various times after treatment by manual neurotomy. Broken lines indicate values from muscles not intentionally treated.



the time 16.4 months have elapsed the magnitudes of all electromyograms have increased still further.

Even when the surgical method of treatment is employed, Billig *et al.* (1) mention the difficulty encountered in limiting the crushing to the fibers supplying a single muscle and suggest that when the manual technique is chosen the possibility of inadvertently manipulating fibers to other than the desired muscle is much greater. The patient from whose muscles figure 3 was constructed also illustrates this point. Although none of the muscles of the forearm innervated by the *ulnar* nerve was intentionally treated, nevertheless changes in potential in these muscles followed the operation. It is also interesting to note that the median nerve fibers supplying some of the forearm muscles were intentionally crushed and that not only did these muscles give evidence of an effect of the operative procedure, but even the muscles of the thenar eminence showed changes in potential, consistent with those found for the more proximal muscles. The apparent explanation for this



observation is that some of the nerve fibers normally making contact with the thenar muscles were interrupted in the course of the treatment, degenerated, and, in the process of branching below the crush and arborizing freely at the muscle, came to supply more muscle fibers and so to give a greater action potential than in the control period. In figure 3 the muscles deliberately treated by neurotomy (solid lines) show greater increases over the control action potentials than those muscles inadvertently affected by the operation

TABLE 1. ACTION POTENTIAL AMPLITUDE CHANGES AT VARIOUS TIMES FOLLOWING NEUROTOMY

MONTHS AFTER OPERATION	AVERAGE CHANGE IN % OF NORMAL ACTION POTENTIAL <sup>1</sup>			% OF MUSCLES WITH GREATER ACTION POTENTIAL AMPLITUDE THAN CONTROL ACTION POTENTIAL SIZE		
	Muscles intentionally treated (A)	Muscles not intentionally treated (B)	All muscles affected by operation (C)	Muscles intentionally treated (D)	Muscles not intentionally treated (E)	All muscles affected by operation (F)
0-4	-15.4	-20.0	-17.3	40.0	25.0	33.3
4-8	+6.4	+21.1	+9.0	58.0	75.0	60.8
8-12	+16.6	+15.8	+16.5	83.3	85.8	84.2
12-18	+24.3	+26.6	+24.9	90.4	75.0	86.4

<sup>1</sup> See page 791 for means of determining these values.

TABLE 2. STATISTICAL ANALYSIS OF ACTION POTENTIAL CHANGES FOLLOWING NEUROTOMY

MONTHS AFTER OPERATION	INTENTIONALLY-TREATED MUSCLES		ALL MUSCLES AFFECTED BY OPERATION	
	Average change in % of normal action potential (A)	$\frac{D^1}{\sigma_D}$ (B)	Average change in % of normal action potential (C)	$\frac{D^1}{\sigma_D}$ (D)
8-18	+21.5	2.67	+21.5	3.32
12-18	+24.3	2.57	+24.9	2.88

<sup>1</sup>  $D$  is the difference between the mean change in % of normal action potential from the controls during the stated interval after operation and the mean change of the 2nd or 3rd controls from the 1st controls (4.0 %).  $\sigma_D$ , The standard error of the difference between 2 means, is derived from the formula:  $\sigma_D = \sqrt{(\sigma_{M_1})^2 + (\sigma_{M_2})^2}$  where  $\sigma_{M_1}$  and  $\sigma_{M_2}$  are the standard errors of the respective means.

(broken lines). Such a finding was not obtained consistently, however, and in 3 of the 4 other patients in whom such a comparison was possible, the reverse was true. That changes in action potential amplitude of muscles not consciously treated by manual neurotomy was a not uncommon finding is shown in columns B and E of table 1, where such results from 23 muscles of 8 patients are summarized.

Tables 1 and 2 present data obtained from the entire group of patients (81 observations on 47 muscles of 20 individuals) and show the following points not already described or obtainable from figure 3. 1) Up to 4 months

after operation most of the muscles studied yield action potentials which are smaller than their respective controls and (except for one case in *column E* of table 1) the proportion of electromyograms of smaller amplitude than the control decreases progressively as the time after operation increases. 2) The average amplitude of muscle action potential which, up to 4 months post-operatively, is less than the control increases progressively (except for one case in *column B* of table 1) after this time until between 12 and 18 months it is approximately 25 per cent greater than before neurotripsy. 3) Eight or more months after neurotripsy the mean increase in percentage of normal action potential over control values is nearly the same whether the muscles deliberately treated are considered separately or whether the group of muscles inadvertently affected is also included (table 1, *columns A* to *C*, and table 2, *columns A* and *C*). 4) Statistical analysis of our data (table 2) shows that the ratio  $\frac{D}{\sigma_D}$  ranges from a minimum value of 2.57 to a maximum value of 3.32.

The smaller ratio indicates that there are only 5 chances out of a thousand that the means of the operated and control groups are not different, while the larger value of  $\frac{D}{\sigma_D}$  shows that the absence of a real difference between

these means would occur less than once in a thousand times by chance. 5) Since, as noted above, the effects of Billig's procedure are not confined to those muscles deliberately treated, and since average action potential values of inadvertently affected muscles do not differ appreciably (8 or more months after operation) from the former group, all muscles affected by the operation may be considered together when evaluating the effectiveness of the operative program as it is applied in actual practice. Accordingly, it may be concluded that 8 months or longer after closed manual neurotripsy those muscles affected by the operation on the average give action potentials which are 21.5 per cent greater than their corresponding controls.

*Effects at the Neuro-myal Junction.* During control electromyographic testing of some of the patients reported in this paper, the amplitude of muscle action potential decreased as a result of brief repetitive maximal motor nerve stimulation or a short bout of voluntary muscular contraction (4, 5). This abnormal response was shown to be due to a defect at the neuro-myal junction. After neurotripsy the impression was gained that this striking reaction was either diminished or abolished in several patients. Unfortunately, well controlled pre- and post-operative records of the muscular response to a volley of skeleto-motor nerve impulses were not available in most cases. Figures 4 to 6 were recorded from the sole surviving motor unit (4, 5) of the short toe flexor of the patient who, prior to operation, gave the most striking evidence of neuro-muscular defect, and in whom sufficient data were at hand

to make a satisfactory comparison between the electromyographic records before and after neurotripsy. Figure 4, taken 8 days before operation, shows the rapid decline of the electromyogram obtained during voluntary plantar toe flexion. Figure 5 is a record from the same muscle of this patient 4.5 months after neurotripsy and demonstrates no such abnormal electrical activity as seen in figure 4. The amplitude of the initial spike in figure 4 is 0.30 mv. (in 2 other controls made on different days the electromyograms obtained were 0.29 and 0.35 mv.), while in figure 5 the first potential of the series is 0.48 mv., thus indicating an increase in the number of muscle fibers

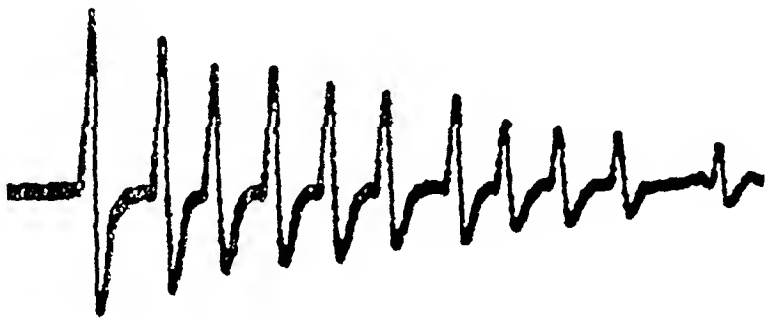


Fig. 4. MUSCLE ACTION POTENTIALS from sole surviving motor unit of the short flexor of the 4th toe of *patient J. H.* during sustained voluntary contraction, obtained 8 days before neurotripsy. Initial spike amplitude is 0.30 mv.; amplitude of final potential shown in record is 0.047 mv., or 16% of the 1st. Time in this and the next figure is 1/60th second between markers at bottom.

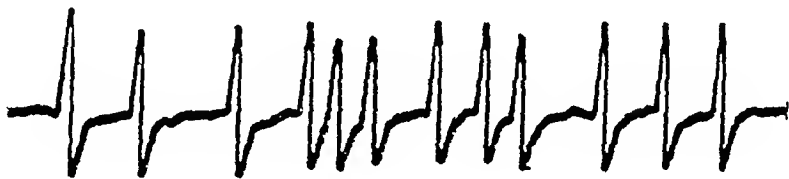


Fig. 5. RECORD OF VOLUNTARY CONTRACTION from same motor unit shown in fig. 4, taken 4.5 months after neurotripsy. The first potential is 0.48 mV. In striking contrast to fig. 4 no potential in the entire record is less than 88% of the height of the 1st, and the final spike is almost identical in amplitude with the 1st in the series.

activated following operation. In figure 6 action potentials secured from this muscle by maximal repetitive stimulation of the tibial nerve (4 times per second) are plotted before (lower curve) and 4.5 months after (upper curve) operation and again show that the neuro-muscular block, which existed before treatment, is not present after neurotripsy.

The manner in which the lessening or abolition of the neuro-muscular block is brought about by the operation under consideration is unknown. It is possible that as a result of the procedure those structures making up the anatomical entity known as the end-plate degenerate, that when the neuro-muscular elements are reconstituted by regeneration they are re-formed

as normal neuro-myal junctions, and that the processes which caused their defect in the first place are either no longer present or fail to exert any detrimental influence on their function.

### DISCUSSION

The subjective improvement noted by the patients and the increased muscle ratings on clinical examination that have been described by Billig and his collaborators (1) are confirmed to some extent by our electromyographic findings, the major difference in results being our failure to find any

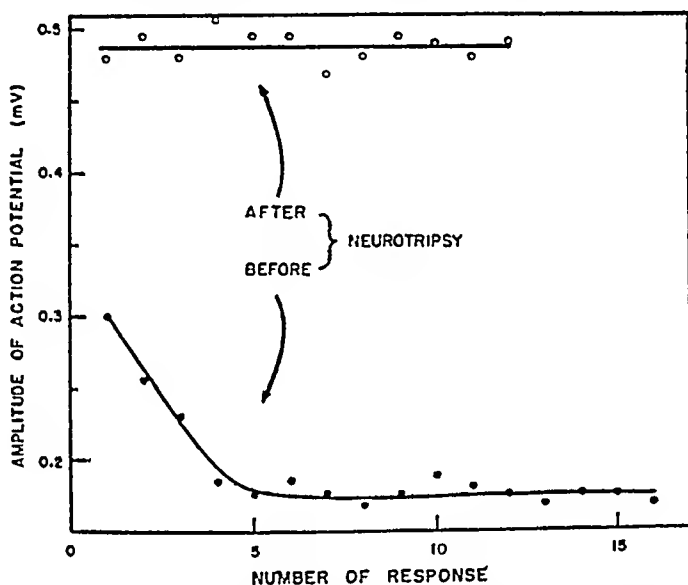


Fig. 6. SAME MUSCLE AND PATIENT as in figs. 4 and 5. Tibial nerve stimulated supramaximally in popliteal space 4 times/second. Abscissa shows the number of the response in a train of stimuli lasting 4 seconds in the lower curve and 3 seconds in the upper curve. Lower curve, before, and upper curve, 4.5 months after operation. No decline in action potential size occurs during repetitive stimulation after neurotripsy.

electrical signs of function, after operation, in a muscle which did not yield action potentials before treatment. For these workers found that many muscles which were rated 'zero' on the control test showed improvement after operation and in a few instances were graded as high as 'poor' after manual neurotripsy.

The following factors should be considered when attempting to explain the contradictory results of the two sets of experiments. 1) Billig's series is larger than ours, and it is possible that with an increased number of observations we would occasionally have found electrical activity following operation where none could be detected prior to the experimental procedure. 2) The absence of action potentials is not necessarily an indication of the complete

absence of motor innervation, since it has been noted (2, 3) that the method employed in these experiments is not always a more sensitive indicator of the presence of a minute amount of innervation than the clinical test of muscle power. However, it should be pointed out that no very large increase in potential following neurotomy could have remained undetected, since we have frequently recorded very small action potentials from muscles in which only a single motor unit remained functional (6).

In spite of the above possible ways of harmonizing discordant findings, the results of Billig's group appear difficult to understand in the light of their own explanation for the improved motor power observed. These workers consider that muscle function increases as a result of branching of a crushed nerve fiber below the point of crush and an increased arborization as the nerve fiber reaches the muscle and branches out to make contact with the muscle fibers (as schematized in fig. 1). Such an explanation, of course, requires the existence of at least one nerve fiber capable of undergoing the changes postulated. And yet Billig's pre-operative muscle tests indicate the *absence*, in 'zero' muscles, of even one functional skeleto-motor nerve fiber, since otherwise these muscles would have been rated as, for example, 'trace.' It is possible that some residual motor innervation does exist in so-called 'zero' muscles and that a block at the neuro-muscular junction prevents the appearance of muscular contraction. Since such a block has been described in poliomyelitis (4, 5) it might be argued that neurotomy in some manner abolishes the defect and allows contraction to become evident. This explanation seems unlikely, since, although abolition of junctional block following neurotomy has been discovered by observation of the changes in the action potentials derived from *one* motor unit, (cf. RESULTS) we have never detected a muscle action potential becoming unmasked after treatment when none existed prior to operation. It would seem logical to expect some observable effect, at least occasionally, in the 'zero' muscles, if a potentially active motor unit were to be de-blocked as a result of operation.

It would, therefore, seem that the simpler explanation of Billig's finding that 'zero' muscles may improve as a result of neurotomy is that the 'zero' muscles were not truly devoid of innervation prior to the operation, but that the minimal innervation available was either not used by the patient or not detected by the examiner.

From our failure to find post-operative improvement in those muscles yielding no muscle action potential on attempted percutaneous nerve stimulation, it is suggested that manual neurotomy in such cases may be of no value and that the patient should not be subjected to this expensive and time-consuming procedure.

In addition to corroborating the belief of Billig *et al* (1) that a larger number of muscle fibers eventually participate in contraction after crushing

the nerve supply of a partially paralyzed muscle than in the control period, we have also found that the neuro-muscular block often observed in chronic poliomyelitis is reduced or abolished in some patients. Both the increase of active muscular elements and the freedom from junctional block would help to account for the statements frequently offered voluntarily by the patients; namely, that they feel stronger and that they tire less easily than before the operation.

It is difficult to state from our data even the average increase in strength to be expected from muscles with some residual innervation treated by Billig's method during the post-operative period studied, for a 21.5 per cent increase in 'percentage of normal potential' (cf. table 2) is not the same if the control muscle is 'trace' as it is if the muscle is rated as 'poor' in the pre-operative test. Since a 'trace' muscle gives an average potential 3.4 per cent of normal, a 'poor' one gives 19.0 per cent and a 'fair' muscle 39.5 per cent of normal action potential amplitude (5), it is clear that a muscle originally rated 'trace' and which increased by 21.5 per cent would now be rated as better than 'poor', or would have increased its grading by more than one full step on Lovett's (7) scale. On the other hand a similar increase of amplitude of action potential in a muscle graded as 'poor' in the control examination would now be classed as 'fair', or have improved by almost exactly one grade. However, since the percentage of normal of muscles with some nervous control intact ranges (in the electromyographic scale (3)) from 3.4 to 100 for the 4 grades lying between 'trace' and 'normal', we may say that an increase in one step corresponds to an increase of  $96.6/4$ , or 24.2 per cent of normal action potential. As a very rough approximation, it may be suggested that muscles affected by operation will average slightly less than a full grade stronger than before treatment, if they are tested 8 or more months after neurotripty.

In such a radical procedure as neurotripty, requiring as it does the damage of existing functional axons, it must be considered whether surgical intervention might result in the permanent impairment of muscular function in some instances. It is believed that such long-range loss of muscle power is unlikely. Out of 48 muscles examined 8 or more months after neurotripty only 7 values were less than the controls. Of these, 3 were less than 5 per cent under the control electromyograms and are probably of no significance because of the known limitations in the accuracy of the method. Furthermore, other muscles studied in these patients at comparable times show electromyograms greater than the controls, the average increase being 27 per cent. The 4 remaining values which were on the average 14.5 per cent less than the control values were obtained from the muscles of 3 patients in whom 18 other muscles studied at corresponding times produced action potentials greater than their respective controls. Also it should be pointed out that 2 of the electromyograms with less amplitude than the controls were from one muscle

of a patient in whom the following sequence was observed: at 4.1 months after neurotomy the particular muscle was 23 per cent less than its preoperative control value, at 11.7 months it was 18 per cent less, and at 16.4 months it was only 12 per cent below the control. Perhaps if this muscle were followed for a longer period it might produce electrical activity which would equal or even exceed that which prevailed before nerve crush. No such analysis was possible for the other values since they were observations obtained at a single interval after neurotomy, but it is not impossible that a similar slow increase to equal or exceed control action potential amplitude might take place if the period of observation were extended sufficiently. It should be emphasized that, although such slow recoveries are possible, they are unusual, since most of the treated muscles are well above control values 8 months after neurotomy (tables 1 and 2) and some have outdistanced the control values in a considerably shorter time, as, e. g., 4 months (fig. 3).

Our findings suggest that the potentialities of neurotomy as a therapeutic measure in poliomyelitis be accorded more serious consideration than has apparently been given it heretofore. The improvement shown is the more significant when it is recalled that it was observed on patients who had shown no change in muscular function in spite of routine physical therapy and other measures for at least a year and usually longer. It is also possible that a selection of the patients treated might result in greater average improvement than reported in this paper, since our data tentatively suggest that moderately paretic muscles tend to show greater functional recovery than do more severely weakened muscles. Finally, the interval between onset of the disease and the operative intervention was long enough in these patients to allow for atrophy and fibrosis of a considerable number of muscle fibers. It is not impossible that even better results than reported here or by Billig and co-workers (1) would result if manual neurotomy were performed before the muscle fibers had regressed to a state in which there was irreversible loss of contractility.

#### SUMMARY

Maximal action potentials elicited by percutaneous nerve stimulation were obtained from the muscles of the extremities of 20 patients in the chronic stage of poliomyelitis. Changes from control action potential amplitude were followed 0.9 to 17.8 months after treatment by the 'closed manual neurotomy' method of Billig. No electrical activity was ever recorded after neurotomy from those muscles which yielded no action potentials before treatment. Changes in action potential size of partially innervated muscles following manual neurotomy were not always limited to those muscles intentionally treated (tables 1 and 2; fig. 3).

Partially innervated skeletal muscles showed a reduction in amplitude

of electromyogram up to 4 months post-operatively, gave slightly greater than the control values from 4 to 8 months after treatment, and on the average yielded action potentials 21.5 per cent larger than the controls from 8 months onward. The increase in action potential size, 8 or more months after operation, was statistically significant when compared with the untreated controls (table 2). The neuro-muscular block which is often observed during repeated motor activity before treatment was either reduced or abolished in some patients after operation. The suggestion is made that neurotripty be considered as a possible useful therapeutic procedure in the treatment of poliomyelitis.

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## *Species Specificity of Agene Toxicity*

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FOR MANY YEARS the syndrome of ataxia, 'running fits,' 'hysterical' states and convulsions, has been recognized in dogs. Various etiologies have been postulated. Within the last two years, evidence has indicated that wheat-protein which has been treated by nitrogen trichloride (agene) is the causative agent. This was discovered by Mellanby (1), who reported that dogs fed an adequate diet containing flour treated with agene developed the syndrome; untreated flour proved harmless. Other investigators (2-5) have confirmed Mellanby's observations and further studies have shown the toxin to be the result of the interaction of wheat and other proteins with agene (2, 3, 5, 6, 7, 14).

The necessity for further investigation of its effects on man became more apparent as the animal experiments proceeded. Because the general population has consumed commercially treated flour for a long time without the appearance of the syndrome, and previous investigations (12-14) have indicated that human subjects of various age groups show no impairment after ingesting moderate amounts of agenized materials, it seemed desirable to test its toxicity on patients subject to seizures.

### MATERIAL AND PROCEDURES

Regular unbleached commercial flour was experimentally treated with agene until the agene level was 150 to 300 gm. of nitrogen trichloride per 100 lb. of flour. This was then baked into bread and cookies. Identical unbleached commercial flour was also baked into bread and cookies for the control ration. The control and experimentally treated baked products were tested on dogs, cats, monkeys and human subjects.

In the case of the animals, each was initially placed on the unbleached control diet and after two weeks shifted to the bleached experimental ration. Both control and experimental diets were supplemented with vitamins and minerals. Careful records were kept of the intake of each animal and in addition daily observations were made to ascertain any change in behavior or neurological status. When an animal was thought to be manifesting abnormality, an acute terminal experiment was performed during which the electroencephalogram was obtained. Control electroencephalograms were taken on several animals fed only a diet containing untreated wheat protein. If an animal showed no clinical abnormality,

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an acute terminal experiment with EEG recording was performed by the time he had eaten half of his initial body weight in agenized baked products. At some time during the electroencephalographic study a respiratory mixture of 30 per cent CO<sub>2</sub> + 70 per cent O<sub>2</sub> was administered in order to see if significant abnormality could be precipitated. Previous study had shown that this gas mixture precipitates seizure discharge in animals that have been fed on agenized proteins and does not produce seizure discharges in animals on a control diet (10).

The subjects chosen were three carefully selected patients (two males, aged 42 and 45 respectively, and one female, aged 25), from the Dixon State Hospital<sup>2</sup>. They were epileptics and were, therefore, presumably readily convulsible. They had seizures only at long intervals, however, and their electroencephalograms were not very abnormal; thus there

TABLE 1. CLINICAL PATHOLOGICAL DATA IN ONE REPRESENTATIVE PATIENT  
No significant alterations in EEG. No increase in incidence of seizures

	CONTROL PERIOD	AT CONCLUSION OF STUDY
<b>URINE</b>		
Specific Gravity.....	1.018	1.024
Albumin.....	0	0
Sugar.....	0	0
Cellular Content.....	none	none
<b>BLOOD CHEMISTRY</b>		
NPN.....	30 mg.%	34 mg.%
Urea nitrogen.....	13.0 mg.%	13.5 mg.%
Creatinine.....	1.3 mg.%	1.3 mg.%
Fasting blood sugar.....	76 mg.%	88 mg.%
<b>HEMOGRAM</b>		
WBC.....	6.88	5.96
RBC.....	5.03	4.86
Differential±.....	normal	normal
Haemoglobin.....	14	13.5
<b>CEREBROSPINAL FLUID</b>		
Pandy.....	negative	negative
Cells.....	none	none
EKG.....	normal	normal
WEIGHT.....	150 #	175 #

was room for an exacerbation of both clinical and electroencephalographic manifestations. They had normal intelligence and were free from other disease. The nature of the investigation was explained to them and their relatives; it was pointed out that agenized protein might play a role in either precipitating or aggravating seizures of predisposed persons. They gladly volunteered for the tests.

Initially anti-convulsant medication was discontinued and each patient was given a physical and nutritional examination. Thereafter, routine hematologic, blood chemical and

<sup>2</sup> Thanks are due to Dr. Warren G. Murray and Dr. Louis Belinson of the Dixon State Hospital for help with the selection of these patients, and to the Director of the Illinois Department of Public Welfare for assistance in contacting relatives and arranging for voluntary transfers to the Illinois Neuropsychiatric Institute.

urinary function examinations were made and repeated during each phase of the experiment. The weight, blood pressure, pulse and temperature of each patient was taken daily and a daily urinalysis was made. In addition, psychological, psychiatric and electroencephalographic examinations were made initially and periodically. The EEG was taken at least every other day and periodic sleep records were obtained.

For the first month the patient was kept on the control unbleached diet. At the end of this period the patient was placed on the experimental diet. All food intake was rigidly supervised and no access was given to food other than that supplied in the prescribed diet. While on the experimental agenized diet the same observations were made as during the control period on the non-agenized diet. When the patients had eaten one-half of their initial body weight in agenized wheat-protein baked products they were repeatedly studied electroencephalographically with and without inhalation of 30 per cent  $\text{CO}_2$  + 70 per cent  $\text{O}_2$ , and then they were taken off the diet. For the next two weeks they were placed on the ward diet, but were still carefully observed to note the development of any sequelae.

During the entire 2 or 3-month period of the study on the 3 patients, the baked product components of the diet were periodically assayed on dogs to note any change in potency of the agenized products. No decrease in toxic action was noted.

### RESULTS

It was found that the ingestion of over one half of the initial body weight of heavily agenized bread and cookies had no ill-effect on these 3 patients with epilepsy. No demonstrable changes could be detected in the EEG; no abnormality in the concentration and albumin content of the urine, as has been reported in the dog (16, 17) was seen; no alteration of the NPN, urea nitrogen, creatine, fasting blood sugar; no changes in the hematogram or the cerebrospinal fluid, and no abnormality of the EKG. There was no increase of seizure activity over that present when the patients were on the untreated control diet. No gross psychological, psychiatric, nutritional or neurological defects resulted from the ingestion of the experimental diet. When given 30 per cent  $\text{CO}_2$  + 70 per cent  $\text{O}_2$  to inhale just prior to the discontinuation of the experimental diet, no grand mal convulsions or seizure discharges were observed.

The cats, monkeys and dogs were fed the identical control and experimental rations as were the patients. Every dog fed the experimental diet showed severe signs of toxicity within 18 hours. Usually only one feeding was necessary. If the animal was allowed to feed again, he died in status epilepticus. Thus, for dogs, the agenized material used in this study was invariably lethal if a quantity equal to 0.04 of the animals' body weight was ingested. All 20 dogs used showed the classical signs of intoxication with agenized material. Their abnormal electroencephalograms could be made worse and seizures induced if a respiratory mixture of 30 per cent  $\text{CO}_2$  + 70 per cent  $\text{O}_2$  were administered.

The 12 cats and 4 monkeys, on the other hand, showed no gross abnor-

malities after ingestion of agenized-baked products even in amounts equal to half their body weight. No tremors or convulsions were noted and the response to carbon dioxide inhalation did not produce seizure activity, although in one cat the EEG did show a few high voltage, slow waves after inhalation of 30 per cent CO<sub>2</sub> and 70 per cent O<sub>2</sub>.

The patients, cats and monkeys gained greatly in weight on the diet of agenized material. The present results are in accord with previous studies (12-14) indicating that man is not injured by diets containing agenized material. In the present study, although the dose of agenized material was greater than has been used heretofore, the patients were unharmed by this amount of agenized bread and cookies which, when adjusted for body weight, was 10 times as great as the lethal dose for dogs.

Conflicting results are reported regarding the susceptibility of cats and monkeys to agene-treated proteins (8, 9, 14, 15, 18, 20). In our experiments, no convulsions, tremors or behavior changes have been noted on the highest doses that were practicable, i.e., 10 times the lethal dose in dogs. Only minimal EEG changes were seen in one cat on the agenized diet after carbon dioxide inhalation.

Next to dogs, it has been found that rabbits and ferrets are most susceptible to agene toxicity (7, 19, 20). On the other hand, rats, guinea pigs, hamsters, mice and chickens, as well as man, show no evidence of susceptibility (1, 7, 14, 15, 17, 18, 20). Monkeys and cats, as mentioned, vary in their reactivity (8, 9, 14, 15, 18, 20).

It would appear that susceptibility to toxic effects from ingested agenized protein is species specific. It seems difficult to conceive of any other explanation for the extremely different responses of man and dog. It remains to be seen whether man has a specific detoxification process for the toxic material, or whether his insusceptibility is the result of distinctly different enzyme systems from those of the dog.

Even dogs seem to be able to ingest 0.1 gm. of NCl<sub>3</sub> plus reacted gluten/kg/dog without toxic effects (11). Only when this level is exceeded do the typical abnormalities appear. It may be that the dog is able to excrete or destroy this amount of toxic material, and that only quantities in excess are beyond its capacity to do so. Thus, the non-susceptibility of other species might be the result of a higher excretion or destruction threshold among other inherent differences.

#### SUMMARY

Human beings already subject to seizures do not develop EEG abnormalities or show an increase in frequency of seizures, or urinary impairment when fed nearly the maximum practicable amounts of highly agenized wheat products for long periods of time. These amounts, adjusted for body weight, are ten times the lethal dose for dogs. Dogs fed this material develop severe

signs within 18 hours after the first feeding. Death ensues within 24 hours after the second feeding. Cats may show slight EEG abnormality on an agenized diet. Reports in the literature indicate that rabbits and ferrets are susceptible to agenized wheat protein, but that rats, mice, hamsters, guinea pigs and chickens show no ill-effects from this. Monkeys vary in their response.

Agenized-protein toxicity is clearly species specific.

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# Effect of Vitamin A<sub>2</sub> on the Red and Blue Threshold of Fully Dark Adapted Vision<sup>1</sup>

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WALD (1) IN 1937 found that the retinae of certain fresh water fish were sensitive especially to red light, whereas the visual systems of most other animals are more sensitive to blue light. The substance in fresh water fish reacting to red light was termed visual red or porphyropsin. It is composed of vitamin A<sub>2</sub> and a protein (2, 3). The more common visual purple such as occurs in the human retina is called rhodopsin. It consists of vitamin A and a protein. Schantz *et al.* (4) showed that vitamin A<sub>2</sub> would replace vitamin A in the visual purple system, blood and liver of the albino rat made previously deficient in vitamin A. The present experiment was based on this work and was undertaken to investigate the physiological activity of vitamin A<sub>2</sub> in the human. The ultimate object was to determine the feasibility of increasing the sensitivity of aviators' eyes to the red lights used for certain military identification and marker service. Normally the human is much more sensitive to blue than to red light. In our experience with 15 normal subjects, there was a 59 per cent (0.39 log unit) greater sensitivity to blue than to red light.

## METHODS AND RESULTS

An adaptometer employing the principles of the Hecht adaptometer for measuring the scotopic vision to red and blue light in the totally dark adapted human being was constructed by members of the Department of Optics of the University of Rochester under the direction of Dr. Brian O'Brien. A system of random testing devised by Selig Hecht was used. The same apparatus and methods were employed by McCann *et al.* (6) in studying the effect of choline hydrochloride on scotopic vision in chronic non-hemolytic jaundice. The subject was fully adapted to the dark for 30 minutes. Binocular vision was centered on a red cross. Interchangeable red and blue filters were inserted. At 7° below the point of fixation, flashes of red and blue light of varying intensities were exhibited for 0.2 second at 5- to 6-second intervals. The random flashes

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were checked by means of a silent shutter which could shut off illumination although the regular shutter clicked. The threshold was that intensity at which 65 per cent of the flashes of light were perceived with each filter.

The subjects were 15 medical students. Eight subjects received pike liver concentrates containing known amounts of vitamin A<sub>2</sub>. This was supplied by Distillation Products, Inc., Rochester, N. Y., under the direction of Dr. Kenneth C. D. Hickman. The vitamin A<sub>2</sub> was assayed by an arbitrary system of units such as that used in measuring vitamin A. Seven subjects took placebo capsules containing corn oil. This contained no vitamin A. (5). After an initial control period all subjects were instructed to follow a diet limited in vitamin A-containing foods. Presumably this restriction was only partial.

At the onset of the experiment, each subject was tested an average of 10 times to familiarize him with the method of testing. Following this, 15 control tests were made in an average of 47 days. Eight treatment subjects then received 13,000 units of vitamin A<sub>2</sub> daily for 72 days; during this period they were tested by the adaptometer an average of 31 times. Since no appreciable change occurred in the thresholds to red and blue light, the dose of Vitamin A<sub>2</sub> was raised to 32,500 U per diem in a second period. This consisted of an average of 39 days with 19 tests per person. During this time the 7 control subjects receiving corn oil underwent a similar number of determinations of dark adaptation. In a final control period all vitamin administration was stopped. This lasted an average of 27 days with 17 tests per person.

*Threshold to Red Light.* As shown in table 1 there was a lowering of the threshold to red light among the 8 students taking vitamin A<sub>2</sub> in doses of 32,500 U per diem. This amounted to 0.20 log unit or 30 per cent in the second period when the larger dose of the drug was used. The greatest individual improvements were in 2 students whose average thresholds fell 0.35 and 0.39 log units or 55 and 59 per cent, respectively. The control subjects showed up to 19 per cent deterioration in their ability to see red light. Both groups tended to revert to normal during the short final control period when all vitamin supplementation was stopped, and a normal diet resumed.

*Threshold to Blue Light.* The control group tended to show some deterioration in sensitivity to blue light during the second treatment period. Otherwise, there was no significant change in either group over the initial control periods in either group.

*Ratio of Red to Blue Threshold.* This figure was considered of significance because it was less affected by daily variations presumably due to fatigue or inattention. Of even more importance, it should provide a measure of the relative amounts of rhodopsin -2 or porphyropsin to rhodopsin -1 (as derived from vitamin A<sub>2</sub> and A<sub>1</sub> respectively) in the retinae of the subjects independent of the absolute amount of vitamin A<sub>1</sub> available in the diet. As shown in table 1 and figure 1 the control group showed little change from

the pre-treatment control period. However, in those persons receiving vitamin A<sub>2</sub> the ratio fell by 25 per cent during the period in which 32,500 U of the vitamin were administered. This represents an improvement of red relative to blue vision. The probability of this being a chance occurrence

TABLE 1. CHANGES OCCURRING IN THE RED AND RED:BLUE THRESHOLDS OF SCOTOPIC VISION IN THE TOTALLY DARK ADAPTED HUMAN EYE

	CONTROL PERIOD	VITAMIN A <sub>2</sub> U/DAY		FINAL CONTROL PERIOD
		13,300	32,500	
<i>Threshold to red light</i>				
Control Group				
Threshold <sup>1</sup> .....	4.072	4.095	4.155	4.111
% change from control period.....		7.5	19.1	8.7
Treatment Group				
Threshold.....	4.272	4.222	3.997	4.046
% change from control period.....		-16.0	-30.1	-21.6
<i>Threshold of red:blue light</i>				
Control Group				
Threshold.....	0.411	0.377	0.396	0.388
% change from control period.....		-8.2	-3.3	-4.9
Treatment Group				
Threshold.....	0.377	0.320	0.253	0.308
% change from control group.....		-12.0	-24.7	-14.4

<sup>1</sup> In log micro micro lamberts.

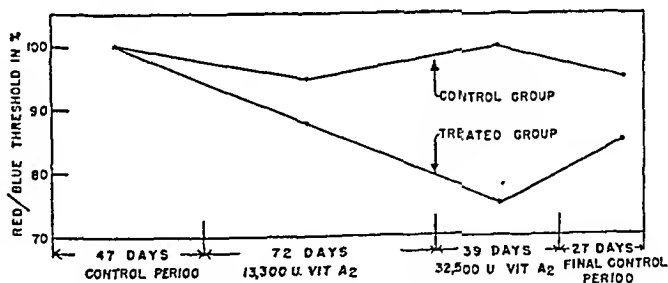


Fig. 1. PERCENTAGE IMPROVEMENT of red: blue light sensitivity.

is considerably less than 1 in 100 (Fisher's  $t = 3.14$  and  $4.53$ ). The greatest individual improvement in this average ratio was 46 per cent. On two occasions this subject was actually more sensitive to red than to blue light.

*Spectral Sensitivity Curves.* These were done under the direction of Dr. Brian O'Brien. There was a slight but apparently significant increased



sensitivity to red light among those persons receiving vitamin A<sub>2</sub>. This did not occur in the control subjects.

*Toxicity.* During the experiment no evidence of toxicity was noted. There were no subjective eye, skin or gastro-intestinal complaints. No anemia or weight loss appeared. Blood vitamin A, calcium, phosphorous, and alkaline phosphatase levels remained normal. A trace of vitamin A<sub>2</sub> was found in the blood of only 1 treated subject. A subject, not included in the experiment, took 90,000 U of vitamin A<sub>2</sub> daily for 2 weeks and exhibited a vitamin A<sub>2</sub> blood level of 1.4 U.

#### SUMMARY

The average threshold at which the totally dark-adapted human eye could perceive red light fell 0.20 log units or 30 per cent in 8 persons receiving vitamin A<sub>2</sub> while on a diet low in vitamin A. Of perhaps more significance, there was a 25 per cent improvement of red in respect to blue vision as well as an increase of sensitivity to red light shown by spectral sensitivity curves. Vitamin A<sub>2</sub> was not toxic in the dosages used. No changes were noted in blood levels of calcium, phosphorous, phosphatase or vitamin A. These results indicate that vitamin A<sub>2</sub> has some physiological activity in human subjects. It is postulated that in the human being, vitamin A<sub>2</sub> may partly replace the vitamin A of visual purple to form visual red.

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## *Phasic Pains Induced by Cold*<sup>1</sup>

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PAIN INDUCED by prolonged and intensive cooling of a distal part, such as a finger, follows a cyclic course. The initial pain soon subsides but will recur again and again if the cold stimulus continues.

It is the purpose of the present report to interpret this curious sensory phenomenon in terms of associated changes in local circulation and neural conduction. The background for the study consists mainly of two earlier and divergent lines of investigation, one concerned with phasic fluctuations in blood flow in a cooled part, the other dealing with the general features of the pain initially noted in response to local cooling.

*Phasic vascular responses to cold* were first described in man by Lewis (1, 2) and later were examined in detail by others (3-8). In all these studies the accompanying sensory changes were virtually disregarded. The accumulated evidence demonstrated that in projecting body areas with relatively large surfaces, such as the digits, nose or ear, there is a brisk vasoconstriction on exposure to cold, due both to a vasomotor reflex and to the direct effect of cold upon arterial walls. Within a few minutes the response is modified to meet the metabolic demands of the chilled tissue, for a well-marked increase in blood flow soon supervenes. This reactive vasodilatation, which Lewis inferred to be an axon reflex, may in some instances be mediated via the vasomotor system (9). After a few minutes, vasoconstriction of variable degree once more is noted; the cycle is resumed and continues at irregular intervals. These adaptive reactions may be regarded as gross exaggerations and distortions of the small spontaneous and rhythmic fluctuations in blood flow which are found in the digits of subjects resting at room temperature (7, 10).

*Pain associated with local cooling* was extensively studied by Wolf and Hardy in experiments in which only the initial pain was observed (11). The occurrence of periodic resur-

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gences of pain during sustained cooling was thus not noted. It was clearly shown that 'cold' pain is separate from the sensation of cold and can be induced only at bath temperatures below 18°C.

Because the amplitude of pulsation of digital arteries was reduced as the pain in a chilled hand rose in intensity, and returned toward control levels as the pain subsided, it was tentatively concluded that vasospasm was in itself painful. The data allowed no additional inferences regarding the source of the pain or the mechanism of the sensory 'adaptation' to cold.

The study herein reported deals with an integration and an extension of these earlier observations. It describes the sequence of events during prolonged exposure of a finger to cold, correlating the course of pain with local vascular reactions and changes in local sensibility. From these data two separate types of 'cold' pain have been identified and their mechanisms postulated. The evidence bears directly upon the question of particular interest: "Is either digital vasoconstriction or vasodilatation per se a source of pain from local cooling?"

#### METHODS

The subjects for this study were 24 adults between the ages of 23 and 48. Twenty were male, and 21 were physicians experienced in the techniques of sensory observations. None of the subjects had vascular disease or neural defects which could significantly have altered the responses to the procedures. A total of 150 experiments was performed. Each subject served at least twice and 3 of the group were used for a majority (ninety-eight) of the experiments.

The observations were made at room temperatures between 23.8° and 27°C. at least 1½ hours after eating the last meal. A digit of one hand of the seated subject was immersed in a large crock of iced water, the water level reaching the middle of the proximal phalanx. The hand was held in this position and approximately at heart level by support of the other digits of the hand upon a wooden shelf and by bracing of the palm against a rubber mat at the margin of the container. The water was maintained at a predetermined temperature, 0°C. for most of the experiments, and was vigorously stirred by a paddle throughout the immersion period. Immersion continued usually through the second rise and fall in pain, i.e., for approximately 20 minutes, but in several experiments lasted for longer periods up to 2 hours.

At 20-second intervals reports were made by the subject of the intensity of any pain noted; the intensities were estimated in units on a 10-point scale, on which 10 represented maximal pain. Each unit was roughly comparable to the 'dol' as defined by Hardy, Wolff and Goodell in studies of discriminable differences in pain evoked by thermal radiation (12). The 2 individuals who served as subjects most frequently were familiar with this basic scale of pain and with the intensity of ceiling (10 dol) pain from a thermal stimulus. Con-

current with the observations of the course of pain, at frequent intervals notes were made of sensibility to touch and superficial pain in the distal phalanx of the immersed digit. Impairments of these modalities were expressed on a crude scale as per cent of normal. Tests of sensibility to deep pain were restricted to a few observations because: 1) it was technically difficult to apply compression to the submerged digit, and 2) such added noxious stimulation tended to induce a lingering ache which obscured the course of cold pain.

In 12 of the experiments photographic records were made of the amplitude of pulsations in the immersed finger by use of a small mechanical plethysmograph. This instrument consisted of a glass chamber connected by pressure tubing to a Frank capsule on which was mounted a small mirror. By means of an optical system deflections of the mirror were recorded upon a moving strip of bromide paper in a camera. At its junction with the proximal interphalangeal joint of the finger, the plethysmograph was sealed with heavy grease. To enhance cooling of the finger the plethysmograph chamber itself was filled with saline before immersion of the part in the cold bath. Although this small jacket of water was thin, it was unstirred. Hence, for effective chilling of the finger to a level equivalent to that obtained when the unprotected finger was immersed in water at  $0^{\circ}\text{C}.$ , a bath temperature of  $-1^{\circ}\text{C}.$  was found necessary.

In a few experiments, some concurrent with the plethysmographic measurements, observations were made of variations in skin temperature on the dorsum of the distal phalanx. The continuously recording thermocouple used for this purpose was connected with a unit in which the galvanometric excursions were amplified and recorded by a photo-electric method.<sup>3</sup>

As a further aid to the analysis of pain mechanisms, the circulation to the immersed finger was interrupted by a sphygomanometer cuff about the upper arm, inflated to 180 to 200 mm. Hg at selected intervals in the pain cycles. For such experiments, the corresponding finger of the opposite hand was simultaneously immersed and served as a control.

## OBSERVATIONS

### *Sensory Phenomena Associated with Cooling of a Finger*

*A. Effects of intense cold ( $0^{\circ}\text{C}.$ ).* Sensory changes during and after immersion of a finger in water maintained at  $0^{\circ}\text{C}.$  were repeatedly observed to follow a general pattern to which there were but few exceptions. In the standard experiment, carried out in 106 trials on 22 subjects, the finger was removed from the bath after complete subsidence of the second cycle of pain. The typi-

<sup>3</sup> This instrument was devised by Dr. R. H. Wallace of Connecticut State College, Storrs, Conn.

cal course of events, plotted graphically in figure 1, can best be described under the following divisions.

**'FIRST' COLD PAIN.** The sensation of cold which began at once upon immersion was joined within 10 to 60 seconds by an aching pain, hereafter termed 'first' pain, which steadily rose to a peak by the end of the 2nd to 4th minute. At its maximum the pain was of high intensity (8 or 9) and was accompanied by distressing tingling lasting a few minutes.

As the pain mounted, impairment of sensibility to touch and pin-prick could soon be detected. This defect became progressively more marked until complete superficial anesthesia and analgesia, at least of the distal phalanx, were noted by the end of the 4th to 7th minute. In the 5th or 6th minute, moreover, the pain and the sensation of coldness began to diminish in intensity,

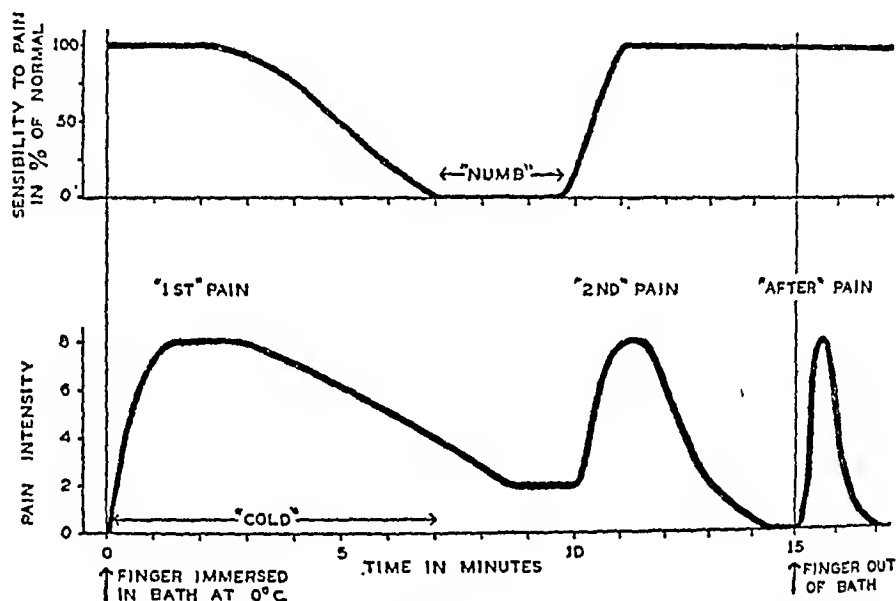


Fig. 1. USUAL COURSE OF PAIN AND CHANGES IN local sensibility in a finger exposed to a water bath at  $0^{\circ}\text{C}$ .

and at about the 10th minute pain was mild and the finger felt neither warm nor cold but completely 'numb.' To tests for both superficial and deep pain the finger was analgesic.

**'SECOND' COLD PAIN.** The period of relative comfort was brief, for within a few seconds a series of changes suddenly intruded, signaled by a return of sensibility in the digit, first in the tip and then throughout the part. Within 15 to 40 seconds pain then commenced a new and precipitous rise to a peak of intensity approximately equal to that of 'first' cold pain. This 'second' cold pain was both a burning and a deep ache and was sometimes slightly throbbing. The maximum was usually reached within 60 seconds, by which time the finger was fully sentient to touch and superficial and deep pain, and felt slightly warm rather than cold. The pain remained briefly at its peak and then slowly sub-

sided until, by the 15th to the 20th minute, all pain was gone. Throughout this phase, however, the sensory modalities remained unimpaired.

'AFTER' PAIN. At this point upon removal of the digit, now moderately reddened, from the bath a final resurgence of pain was noted. Such 'after' pain began within 15 seconds and achieved its peak of a moderate or severe intensity even more rapidly than did the 'second' cold pain. Like the latter it was a deep ache with a burning quality but more evidently throbbing and associated with a distinct sensation of local heat. The pain lasted less than 2 minutes and as it vanished the erythema slowly faded, but the finger gradually rose in temperature until it became manifestly warmer and pinker than its fellows and slightly tender, remaining so for many minutes thereafter.<sup>4</sup>

For any one subject the maximal intensity of 'first' cold pain and the time of onset of 'second' cold pain were nearly reproducible on repeated experiments; the intensities of 'second' and 'after' pains were less predictable. The range of inter-individual variations in all these features was wide.

ATYPICAL REACTIONS. In 2 of the 22 subjects of this standard experiment, no 'second' cold pain was noted despite the return of digital sensibility at the usual time. Yet repetitions of the experiment at later dates and using the same digit yielded typical pain patterns. In 3 other subjects the cyclic pains were considerably delayed or prolonged. 'After' pain in 1 individual did not begin until 80 seconds after the digit was removed from the bath and persisted for 6 to 7 minutes. This subject, a male aged 25, has long noted that his hands become unduly moist and cold under tension. In 2 other males with ostensibly normal circulatory reactions in their hands, 'second' cold pain failed to subside in the usual fashion but held at moderate or high intensity until the cooling was discontinued after 32 to 41 minutes.

ADDITIONAL PAINS DURING PROLONGED IMMERSION. In 19 experiments involving 7 subjects the finger was kept in the water bath at 0°C. well beyond the end of the 'second' cold pain and for periods up to 2 hours. Under these conditions pains of variable intensity and duration occurred irregularly at 3 to 18 minute intervals. Although usually mild and fleeting, each of these added pains seemed analogous to 'first' cold pain, for in general every recurrence was foreshadowed and accompanied by a sensation of coldness in the finger. And if the pain reached a moderate or high intensity, progressive impairment of sensibility could be demonstrated; occasionally the numbness became as complete as was noted with 'first' cold pain. Subsidence of each of these pains was accompanied by a return of whatever sensibility had been lost. In no instance, however, did this change precipitate a burning and warm ache such as

<sup>4</sup> A single experiment with cooling of a toe at 0°C. yielded pains comparable to those elicited in a finger, although the first phase of the cycle was greatly prolonged. 'First' cold pain subsided completely by the 5th minute and the toe remained painless and analgesic until the onset of 'second' cold pain at 22 minutes. 'After' pain was particularly intense.

followed 'first' cold pain. A representative series of such pains, together with plethysmographic data to be discussed in a following section, is graphed in figure 2.

In the most sustained period of cooling, 127 minutes in length, 25 separate pains occurred, but only 7 of these were severe. It was repeatedly observed that after prolonged immersion and numerous such cyclic pains the 'after' pain on withdrawal was likely to be mild and unusually brief.

Contrary to expectation no untoward after-effects were experienced in the finger following such prolonged noxious stimulations. Some subjects noted

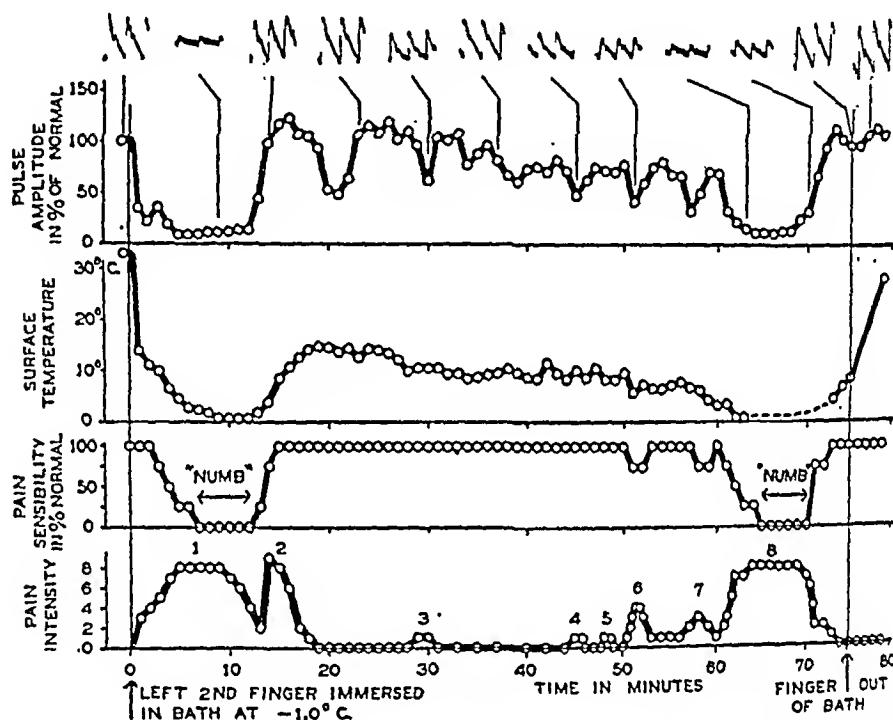


Fig. 2. REPRESENTATIVE GRAPH OF COURSE OF PAIN, local sensibility, surface temperatures and pulse amplitudes in a finger exposed to intense cold for 75 minutes. The water bath at  $-1^{\circ}\text{C}$ . cooled the plethysmograph-encased digit to a degree approximately equivalent to immersion of an unprotected digit at  $0^{\circ}\text{C}$ . Samples of the plethysmograms are shown at the top of the graph.

mild arthralgia and tenderness persisting for 1 to 2 days, but this was as likely to occur after a short experiment as after a long one.

In the course of several of the experiments a few subjects developed a brief pre-syncope reaction, characterized by giddiness, profuse sweating, facial pallor, and sometimes bradycardia. Such a reaction was most commonly noted during the decline in 'second' cold pain. In other respects its occurrence was unpredictable and could not be related to the intensity of the pains experienced or to any unusual attitude of the subject to the experimental situation.

*B. Effects of moderate cold ( $3^{\circ}\text{C}$ .– $10^{\circ}\text{C}$ .).* The sensory responses of a finger immersed at various bath temperatures between  $3^{\circ}$  and  $10^{\circ}\text{C}$ . were observed in

14 experiments on 2 subjects. At temperatures of  $5^{\circ}$  or above, 'first' cold pain was less intense and usually briefer than at  $0^{\circ}$  and was accompanied by only mild hypesthesia and hypalgesia. A return of full sensibility coincided with the subsidence of 'first' cold pain and was not followed by a 'second' cold pain. A short-lived and mild 'after' pain was noted when the immersion was discontinued, but this was absent at bath temperatures above  $7^{\circ}\text{C}$ .

Prolonged immersion induced repeated slight resurgences of pain with slight reductions in sensibility, similar to, but minor versions of, the cyclic reactions noted at  $0^{\circ}\text{C}$ .

### *Correlations of Sensory and Circulatory Phenomena of Cooling*

Plethysmographic records of pulses in the chilled finger, supplemented in some instances by measurements of surface temperature, were made in 12 experiments on 4 subjects. The local circulatory responses to cold were found to bear a predictable relationship to each of the phasic pain responses.

A representative series of observations is shown in figure 2. At the water bath temperature of  $-1^{\circ}\text{C}$ . (a stimulus approximately equivalent to immersion of the unprotected digit at  $0^{\circ}\text{C}$ .) the pulse amplitude of the chilled finger was greatly reduced during the first few minutes of immersion. In the instance illustrated, the pulse was reduced to 9 per cent of the control level, indicating an extreme degree of vasoconstriction; there was a concurrent but unmeasured decrease in finger volume. In this same period the skin temperature on the dorsum of the distal phalanx fell rapidly from  $33.0^{\circ}$  to  $0.5^{\circ}$ . 'First' cold pain was at its maximum intensity at this latter point. It was noted that the order of events late in 'first' cold pain began with a partial release of vasoconstriction, leading to a return of sensibility in the finger. This was followed by a further increase in pulse amplitude to control levels or somewhat above, accompanied in the experiment cited by a rise in surface temperature to  $14.7^{\circ}\text{C}$ . 'Second' cold pain appeared and reached its peak while the latter changes were taking place.

There was thereafter a slow and halting diminution in pulse volume and finger temperature. Mild and fleeting pains accompanied brief further vasoconstrictions, culminating at the end of an hour in an intense 'seventh' cold pain similar in every way to 'first' cold pain. The subsequent return of circulation and sensibility, however, was painless; no analogue to 'second' cold pain developed. 'After' pain upon removal of the finger from the bath also was absent.

In these experiments, although the reactive increase in pulse amplitude with 'second' cold pain commonly surpassed control levels, the maximum was sometimes reached after 'second' cold pain had subsided, and there were several instances in which the pulse amplitude rose only to, but not above, normal.



### *Modifications of Course of Cold Pains by Induced Circulatory Arrest*

A closer analysis of the components in the waxing and waning of cold pains was made possible by a series of experiments in which the circulation to the hand was interrupted at selected points in the cycle.<sup>5</sup> The 24 experiments in which circulatory arrest was thus induced by a cuff around the upper arm were carried out on 4 subjects. In each of these individuals typical patterns of pain had previously been clearly demonstrated. The results of the analysis can be organized under the following sections.

*A. 'First' cold pain.* The effects of such induced ischemia upon 'first' cold pain depended upon the intensity of the cold stimulus. In tests at 0°C. inflation of the occlusive cuff immediately prior to immersion of finger failed

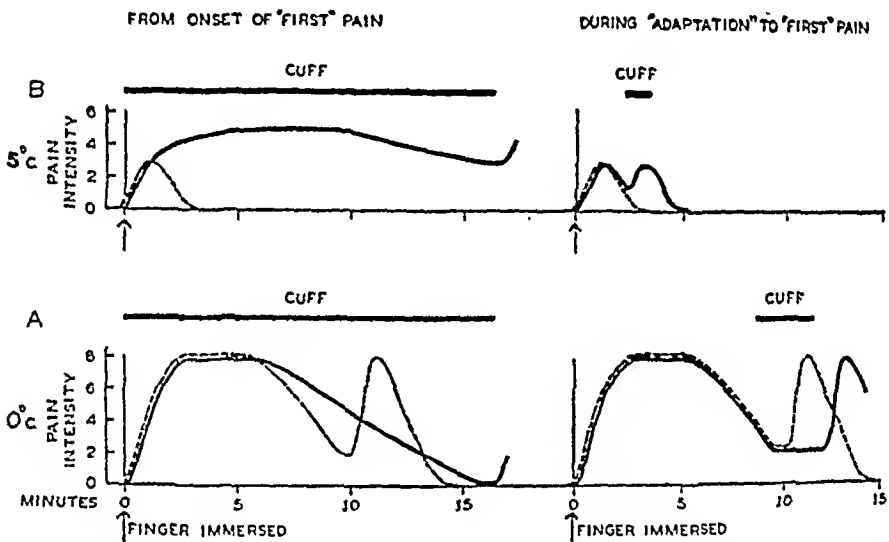


Fig. 3. DIAGRAMMATIC ANALYSIS OF NEURAL AND VASCULAR factors in 'first' cold pain by means of induced circulatory arrest: A, at 0°C., and B at 5°C. The normal course of 'first' pain, as observed in a control finger, is plotted by an interrupted line. The course of 'first' pain in the test digit is shown by a solid line.

to alter the usual rise and fall in 'first' cold pain or the development of digital anesthesia and analgesia except for a slight slowing of the usual rate of subsidence of the pain. Furthermore, when the circulatory block was inserted instead during the fall in the curve of 'first' cold pain, the pain continued to decline in usual fashion. These results, together with the course of pain in a control digit simultaneously immersed, are outlined diagrammatically in figure 3A.

<sup>5</sup> The circulatory stasis distal to a cuff compressing the arm is not as complete as was assumed by earlier investigators. For Weddell and Sinclair (13) have shown that a sluggish and intermittent flow can be detected in the capillaries of the nail-bed even though the cuff encircling the arm be inflated to pressures well above the systolic level. This leakage, which may occur through deep and protected vessels, such as those of the bones, is probably of little significance, for the gross effects observable in the limb clearly indicate severe circulatory arrest.

In contrast, under less vigorous cold stimulation, as at  $4^{\circ}$  or  $5^{\circ}\text{C}.$ , the inflation of the cuff prior to chilling of the finger greatly modified the pain response. 'First' cold pain under these circumstances reached a much higher intensity and was far longer sustained than in a control digit, and subsided only as the ischemic finger became analgesic after 28 minutes. Upon release of the cuff at this point, a 'second' cold pain of unusual severity was noted, together with the intense tingling customarily associated with recovery from prolonged neural ischemia (13, 14). When the circulatory block was introduced during the decline in 'first' cold pain, 'adaptation' was then reversed, for the pain rose promptly and soon reached the initial peak (fig. 3B).

These findings indicate that ischemia induced by an occlusive cuff about the arm may have little effect upon the course of 'first' cold pain when the cold stimulus is very intense. For at bath temperatures near  $0^{\circ}\text{C}.$  the vasoconstriction induced by cold seems so effectively to curtail digital circulation that added circulatory arrest by a cuff means little. It may be inferred also that 'adaptation' to 'first' cold pain at  $0^{\circ}\text{C}.$  is principally or entirely neural, i.e., attributable to the local analgesia which follows cooling and vasoconstrictive ischemia.

The location of the block to pain perception in intensely cooled tissue, whether at pain endings or in the nerve fibres themselves, is uncertain. But that cold is neuroparalytic has been well established, not only by Gasser in studies of nerve conduction in the frog (15) but also by Bickford in observations upon man (16). The latter has shown that cold applied to a nerve trunk is initially painful but that loss of pain perception and other sensory modalities later ensues. It has clearly been demonstrated, moreover, that ischemia is not essential to this process, nor will ischemia alone produce analgesia so readily as does cold.

Less intense chilling, as at  $5^{\circ}\text{C}.$ , induces only a moderate vasoconstriction; if the resultant ischemia then be made maximal by circulatory arrest in the arm, the cooling of the finger is enhanced and 'first' pain is augmented, a phenomenon noted a decade ago by Lewis and Pochin (17). The subsidence of 'first' pain at  $5^{\circ}$  is principally a circulatory affair, i.e., it is accompanied by only trivial hypalgesia and by a progressive release of vasoconstriction and rewarming of the finger. Hence, the 'adaptation' is halted and reversed if local circulation is cut off by inflation of the arm cuff.

The actual mechanism by which the cold stimulus evokes pain is still not adequately defined. Inasmuch as cold induces local erythema and may impair neural conduction, it is literally a noxious agent, but the exact site of its painful action remains in doubt. It is likely that the pain arises by direct excitation either of pain fibres or of their endings by a metabolite released from injured tissue. These two possibilities are not mutually exclusive, and indeed may involve essentially similar chemical processes.

The data do not justify an inference that digital vasoconstriction from cold is in itself painful (11). They do suggest that the vasoconstriction accompanying 'first' cold pain is relevant in that it promotes tissue cooling and thus enhances the intensity of the cold stimulus.

*B. 'Second' cold pain.* Upon interruption of circulation in the arm during the development of 'second' cold pain (at 0°C.) the pain consistently rose to a higher intensity and lasted longer than did concurrent 'second' cold pain in the control finger. The return of sensibility to touch and pain which is normally so early and prominent a part of the 'second' cold pain cycle was quickly halted and soon reversed. A feeling of coldness was also soon evident, and sensation seemed to be traversing once more the curve of 'first' cold pain.

Inflation of the arm cuff during subsidence of 'second' cold pain led at once to a temporary resurgence of pain and, as above, a sensation of coldness and a slowly developing insensibility.

These procedures were designed to test the thesis that the reactive vasodilatation which accompanies 'second' pain might be a direct source of the pain. They were based upon the observation that local circulatory arrest may diminish the pain of arterial distention elsewhere in the body, as when compression of a temporal or carotid artery temporarily alleviates certain forms of headache. In these experiments, however, arterial compression proved to be an indecisive test, for inflation of the arm cuff at once so enhanced cooling of the immersed finger that the events of 'first' pain were repeated, thus masking the analysis of 'second' pain.

Other pieces of evidence were also inconclusive. As shown by the plethysmograms, of which figure 2 is typical, the digital pulse amplitude during 'second' pain rose only slightly above control levels and in some instances was maximal after the pain had entirely subsided. Equally pertinent is the report that the injection of such potent vasodilators as papaverine, meholyl or histamine into the brachial or femoral artery does not produce pain (18). Nonetheless, it remains possible that after injury to vessel walls by cold and ischemia, a mild and normally painless degree of vasodilatation now evokes pain.

An alternative hypothesis is suggested by Zotterman's demonstration that the excitability of an excised and asphyxiated nerve is temporarily increased when the nerve is resupplied with oxygen (19). Furthermore, even gentle warming of an ischemic finger will give rise to pain (20). It is likely, therefore, that during the reactive vasodilatation which follows 'first' cold pain, the return of function in sensory nerves previously numbed by cold and ischemia might in itself be a transiently painful process. This question was explored further in the following manner.

In 3 experiments upon 2 subjects a finger to which the circulation was arrested by an arm cuff was held immersed in a water bath at 0°C. until 'first' cold pain had subsided and the digit was apparently completely insensible.

Mild warming of the ischemic digit was then induced by transfer to a water bath at either 37° or 40°C. This procedure led within 15 seconds to an exceedingly intense burning and aching pain, coincident with a partial return of sensibility to touch and pin-prick in the finger.

Thus merely by rewarming, pain can be evoked from tissue which has been deeply cooled during sustained circulatory arrest. This apparent renewal of local tissue metabolism, including neural activity, in response to warming seems highly pertinent to the phenomenon of 'second' cold pain. As Lewis originally suggested, a noxious metabolite may be formed in tissue damaged by cooling and ischemia (21). Rewarming may transiently increase the release of this hypothetical 'P' substance at the same time as it leads to restoration of nerve function. The combined effects are detected as pain, which persists until the metabolite is washed away or the tissue injury subsides. Indirect evidence has tentatively identified the potassium ion with the 'P' substance, but its role remains unproven (18).

Throughout digital chilling the arterial blood in the arm or forearm is exposed to cooling in transit by the returning blood in the adjacent *venae comites*. As shown by Bazett *et al.* this interchange of heat is enhanced during the period of peripheral vasodilatation which follows exposure to cold (22). The fall in temperature thus induced in the limb arteries, such as the radial, is probably most marked immediately prior to 'second' pain. It is relatively small, however, and is unlikely to be of significance in the mechanism of the 'second' pain, particularly since during this phase the temperature of the cooled digital tissues is actually rising.

The absence of pain accompanying release of marked vasoconstriction late in the course of digital cooling at 0°C. (as after 'seventh' cold pain in fig. 2) is not readily explained. This apparently anomalous finding may be related to a slower return of circulation and neural function, or to the development of adaptive changes of unknown nature in the tissue.

*C. Additional cycles of pain in prolonged immersion.* Inflation of the arm cuff during the resting phase after subsidence of 'second' cold pain promptly induced a cold ache comparable in quality and intensity to 'first' cold pain, and accompanied by increasing hypesthesia and hypalgesia. Such episodes could be repeatedly precipitated by brief circulatory arrests spaced at random in pain-free intervals in the immersion period.

The pains secondary to such experimentally induced ischemia appear clearly to be the analogues of spontaneous 'third' cold pain and those which follow later in the usual cycle. And like 'first' cold pain these all depend upon a reduction in local circulation, permitting deep cooling of the digit. The intensity of each such later spontaneous pain, as the plethysmographic record of figure 2 shows, is related to the degree and duration of the vasoconstriction which precedes and accompanies it.

*D. 'After' pain.* When the circulation was interrupted by the cuff following 'second' cold pain and immediately prior to removal of the digit from the 0°C. bath, the usual 'after' pain was prevented. Upon deflation of the cuff 3 minutes later a brief pain occurred, of somewhat less intensity than the 'after' pain which had been noted in the control finger.

Inflation of the cuff during a rise in 'after' pain induced a decrease in its intensity of variable degree, beginning in 15–20 seconds. This was followed by a brief resurgence of pain when the cuff was released.

The intensity of 'after' pain was reduced more effectively by re-immersion of the digit in the cold bath, for the procedure abolished the pain completely within 40 seconds; the pain recurred as soon as the finger was withdrawn from the water bath.

The similarities of 'after' pain to 'second' cold pain are evident, for both are associated with a feeling of warmth in a digit in which the blood supply is increasing and tissue temperature is rising. 'After' pain, however, is less complex a reaction, for it is not associated with the added factor of returning function in sensory nerves, and can be reduced in intensity by procedures which retard the warming of the finger. Since the pain is alleviated more effectively by recooling in the bath than by circulatory arrest, it can be postulated that 'after' pain is due primarily to the rapid warming of recently damaged tissue, a process known to be painful even when the injury is mild (20). Whether the marked vasodilatation which follows withdrawal of the digit from the cold bath also contributes to the pain remains uncertain.

#### DISCUSSION

In the pain cycles induced during local chilling, as in a digit, 2 separate processes have been identified: one is associated with deep cooling enhanced by ischemia; the other is associated with partial rewarming and vasodilatation. It is only the former mechanism which can accurately be termed cold pain; its intensity parallels the degree of effective cooling unless the cooling becomes sufficient to block sensory nerve conduction.

A corollary to the present observations on normal subjects is found in the studies by Kellgran *et al.* of cold pain induced in injured tissues (23). When tissue damage is sufficient to produce deep hyperalgesia, as after a fracture, the threshold to cold pain may be very low. This vulnerability is partly due in many instances to impaired circulation in the part (and is abolished by sympathectomy) but sometimes is attributable solely to the local deep hyperalgesia.

Cold pain finds another clinical counterpart in the experience of the patient with Raynaud's disease. Because of excessive vaso-spasm his digits are unusually susceptible to pain from low environmental temperatures. But as Lewis has emphasized, most of the pain of this disorder is experienced when the hands are warmed after even mild cooling (21). This, then, is pain analo-

gous to the 'second' pain of the experimental cycle, a pain associated with rapid rewarming of previously cold and ischemic, and thereby damaged, tissue. The occurrence of such pain can perhaps be interpreted as a sign that too abrupt a return of blood flow, warmth and oxygen may be injurious. Clinical experience in instances of frank tissue damage, as in frostbite, supports this contention, for under such conditions anatomic recovery is optimal if the rate of rewarming is greatly retarded.

#### SUMMARY

From analyses of local vascular and sensory changes, 2 separate kinds of pain can be identified in a finger cooled in a water bath. The principal type, of which the 'first' pain is representative, is properly termed 'cold' pain. It is associated with a vasoconstriction which enhances cooling of the finger, but there is no evidence that the vasoconstriction is in itself a source of pain. The pain can be attributed to direct injury to the chilled tissues or nerves and may be mediated by a metabolite locally released. In sustained exposure to cold, recurrent pains of the same type are noted.

Another and separate type of pain from cooling, namely 'second' pain, occurs only during the phase of recovery from the marked vasoconstrictive ischemia induced by intense cooling, as at bath temperatures below 5°C. It is associated with reactive vasodilatation and a consequent warming of the finger and return of function in sensory nerves earlier paralyzed by cold. A contribution of pain from dilatation of injured vessels is conjectured but is unproven. 'After' pain, following soon upon withdrawal of the digit from the cold stimulus, is a subvariety of 'second' pain, but return of sensibility in the part is here not a factor.

These phenomena are relevant to the unusual susceptibility to cold pain commonly noted in 2 clinical syndromes: in injured tissues with deep hyperalgesia (sometimes accompanied by impairment of local circulation), and in the digits of the patient with Raynaud's disease.

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# *'Ideal' Alveolar Air and the Analysis of Ventilation-Perfusion Relationships in the Lungs<sup>1</sup>*

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THE ANALYSIS OF BLOOD-GAS RELATIONSHIPS in the lungs is handicapped by ambiguity regarding the concept of alveolar air (1). It is well known that patients suffering from pulmonary diseases may have alveolar air which varies in composition in different parts of the lungs (2, 3), yet there has been no adequate way of defining the composition of alveolar air under such circumstances. Furthermore, the relationships between alveolar ventilation and alveolar perfusion with blood, which are primary factors in determining the composition of the alveolar air, have been dealt with only in general terms. The purpose of this paper is to discuss a specific definition of alveolar air which is applicable to both normal and pathological conditions, and, with the help of this concept, to outline a system of analysis of ventilation-perfusion relationships in health and disease.

## SCHEMATIC REPRESENTATION OF VENTILATION, PERFUSION AND GAS EXCHANGE

The cyclic nature of the ventilatory process tends to obscure certain fundamental relationships between alveolar air and the blood in the alveolar capillaries. Let us therefore consider a schematic representation of ventilation, perfusion and gas exchange in which these processes are conceived of as continuous (fig. 1). Inspired air and mixed venous blood pass into the alveoli where they approach equilibrium with respect to partial pressures of oxygen and carbon dioxide by diffusion of gases across the pulmonary membrane. The blood leaving the alveolar capillaries is modified slightly by the admixture of a small amount of venous blood which can be thought of as a shunt. The alveolar air leaving the alveolar spaces is modified by the admixture of dead space air, which has the composition of inspired air and may also be thought of as a shunt.

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# FUNDAMENTAL RELATIONSHIPS BETWEEN RESPIRATORY GASES IN THE BLOOD AND IN THE ALVEOLAR AIR

The quantity of carbon dioxide added to the alveolar air is the same as the quantity given up by the blood, and the quantity of oxygen given up by the alveolar air is the same as that added to the blood. Hence:

$$V_a \times (AL - I) \text{ in } \%CO_2 = P \times (V - C) \text{ in vol. } \%CO_2$$

$$CO_2 \text{ added to alveolar air} = CO_2 \text{ given up by blood.} \quad (1)$$

$$V_a \times (I_e^2 - AL) \text{ in } \%O_2 = P \times (C - V) \text{ in vol. } \%O_2$$

$$O_2 \text{ given up by alveolar air} = O_2 \text{ taken up by blood.} \quad (2)$$

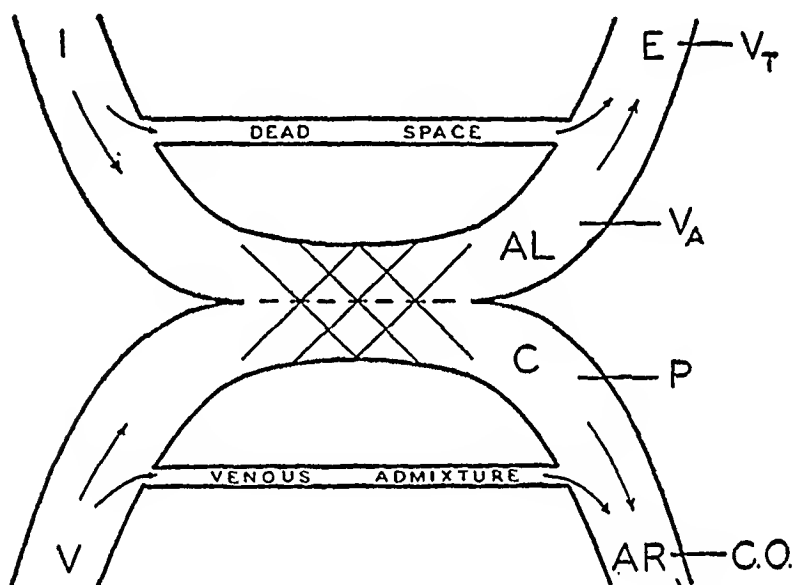


Fig. 1. SCHEMATIC REPRESENTATION of ventilation, perfusion and gas exchange. I = inspired air; AL = alveolar air; E = expired air; V = mixed venous blood; C = blood leaving the alveolar capillaries; AR = mixed arterial blood;  $V_t$  = total ventilation;  $V_a$  = alveolar ventilation, i.e. alveolar air flow; P = perfusion with blood, i.e. alveolar capillary flow; C.O. = cardiac output.

The ratio of alveolar ventilation to alveolar perfusion with blood may be expressed as a rearrangement of equations (1) and (2):

$$\frac{V_a}{P} = \frac{(C - V) \text{ in vol. } \%O_2}{(I_e^2 - AL) \text{ in } \%O_2} = \frac{(V - C) \text{ in vol. } \%CO_2}{(AL - I) \text{ in } \%CO_2} \quad (3)$$

$$^2 I_e = \text{insp. } \%O_2 + \frac{\text{alv. } \%CO_2 \times \text{insp. } \%O_2 \times (1 - R.Q.)}{100 \times R.Q.}$$

where insp.  $\%O_2$  =  $\%O_2$  in inspired air,

alv.  $\%CO_2$  =  $\%CO_2$  in alveolar air.

Inspired air  $\%O_2$  is corrected in this way in order to take into account the difference in volume between inspired air and alveolar air. The first half of equation (4) then becomes equivalent to equation (12) below, when I in  $\%CO_2$  = 0.

The ratio of carbon dioxide exchange to oxygen exchange, i.e. the respiratory quotient (R.Q.), may be expressed as another rearrangement of equations (1) and (2):

$$\text{R.Q.} = \frac{(\text{AL} - \text{I}) \text{ in } \% \text{CO}_2}{(\text{I}_c - \text{AL}) \text{ in } \% \text{CO}_2} = \frac{(\text{V} - \text{C}) \text{ in vol. } \% \text{CO}_2}{(\text{C} - \text{V}) \text{ in vol. } \% \text{O}_2} \quad (4)$$

Gas R.Q. Blood R.Q.

#### CONCEPT OF 'IDEAL' ALVEOLAR AIR

The fundamental equations provide a means of defining precisely what the composition of the alveolar air and the blood leaving the alveolar capillaries would be if these values were homogeneous throughout the lungs and if perfect equilibrium were reached between the blood and gas phases. This statement is based upon the following considerations.

If the subject is in a steady state, the composition of the inspired air entering the alveoli and of the mixed venous blood entering the alveolar capillaries is constant throughout all parts of the lungs and can be determined by direct sampling and analysis. On the other hand, the composition of the alveolar air and of the blood leaving the alveolar capillaries is variable, depending upon ventilation-perfusion relationships as indicated by equation (3). Each different value for alveolar air and alveolar capillary blood is associated with a different value for R.Q., as indicated by equation (4). At the specific R.Q. which applies to the lung as a whole, there is only one value of alveolar and capillary  $\text{pCO}_2$  and of alveolar and capillary  $\text{pO}_2$  which satisfies both the gas R.Q. and the blood R.Q. equations. This one value, which we shall call the 'ideal' value, is therefore the only value which could exist homogeneously throughout all parts of the lungs and still be compatible with the quantitative aspects of gas exchange which actually exist in a given subject.<sup>3</sup>

#### DETERMINATION OF 'IDEAL' ALVEOLAR AIR

The mathematical derivation of the 'ideal' alveolar point requires that the blood and gas R.Q. equations both be expressed in terms of partial pressure since it is only in these terms that the identity between alveolar air and the blood leaving the alveolar capillaries exists. Because of the difficulty in changing units in the case of the blood R.Q. equation, the derivation is more easily presented graphically.<sup>4</sup>

<sup>3</sup> Essentially this same concept has been arrived at independently by H. Rahn (personal communication).

<sup>4</sup> The mathematical demonstration that there is a unique solution to the blood and gas R.Q. equations when the subject is in a steady state is complicated by the necessity for using equations for the  $\text{CO}_2$  and  $\text{O}_2$  dissociation curves of blood. However, under the guidance of Dr. Domingo Gomez, the following steps have been outlined:

Equation (4) may be divided into the gas and blood R.Q. equations, respectively. The change

The graphic determination of 'ideal' alveolar air is based in part upon the work of Fenn, Rahn and Otis (4). These authors showed that when  $p\text{CO}_2$  and  $p\text{O}_2$  were used as coordinates, different R.Q.'s could be plotted as straight lines radiating from a point representing moist inspired air. It can be seen from *equation (4)* that the slope of the R.Q. lines is determined by the ratio  $\frac{(\text{AL} - \text{I}) \text{ in } \% \text{CO}_2}{(\text{I}_c - \text{AL}) \text{ in } \% \text{O}_2}$ . In figure 2 several R.Q. lines have been plotted using a normal value for moist inspired air at body temperature and pressure ( $p\text{O}_2 = 150 \text{ mm. Hg}$ ;  $p\text{CO}_2 = 0$ ).

The consideration of alveolar ventilation and alveolar perfusion as parallel phenomena led to the realization that data regarding blood in the alveolar capillaries can be plotted in a manner similar to the alveolar air. When the second half of *equation (4)* is used it is found that if vol.  $\% \text{CO}_2$  and vol.  $\% \text{O}_2$  are chosen as coordinates, then lines representing different blood R.Q.'s may be drawn. These lines radiate from the mixed venous blood point (V) and have a slope which is determined by the ratio  $\frac{(\text{V} - \text{C}) \text{ in vol. } \% \text{CO}_2}{(\text{C} - \text{V}) \text{ in vol. } \% \text{O}_2}$ . In figure 3 several blood R.Q. lines are plotted, using values for the composition of mixed venous blood which were obtained by cardiac catheterization in a normal subject ( $\text{O}_2$  content = 13.2 vol.  $\%$ ;  $\text{CO}_2$  content = 54.1 vol.  $\%$ ).

The normal individual under consideration had an R.Q. of 0.8. Thus,

of units in *equation (5)* is permissible because the relationship between percentage and partial pressure is linear in the gas phase.

$$(\text{AL} - \text{I}) \text{ in } p\text{CO}_2 = \text{R.Q.} \times (\text{I}_c - \text{AL}) \text{ in } p\text{O}_2 \quad (5)$$

$$(\text{V} - \text{C}) \text{ in vol. } \% \text{CO}_2 = \text{R.Q.} \times (\text{C} - \text{V}) \text{ in vol. } \% \text{O}_2 \quad (6)$$

*Equation (6)* must now be expressed in terms of partial pressure in order that the identity between alveolar and capillary tensions may be used in solving for alveolar  $p\text{CO}_2$  and alveolar  $p\text{O}_2$ . The following symbols will be used:

For the gas phase,

$$\text{AL in } p\text{CO}_2 = p\text{CO}_{2\text{AL}}$$

$$\text{I in } p\text{CO}_2 = p\text{CO}_{2\text{I}}$$

and

$$\text{AL in } p\text{O}_2 = p\text{O}_{2\text{AL}}$$

$$\text{I}_c \text{ in } p\text{O}_2 = p\text{O}_{2\text{I}_c}$$

For the blood phase, in general,

$$\text{vol. } \% \text{CO}_2 = f(p\text{CO}_2)$$

and

$$\text{vol. } \% \text{O}_2 = F(p\text{O}_2),$$

where  $f$  and  $F$  are 2 different functions describing the  $\text{CO}_2$  and  $\text{O}_2$  dissociation curves, respectively.

Specifically,

$$\text{V in vol. } \% \text{CO}_2 = f(p\text{CO}_{2\text{V}})$$

$$\text{V in vol. } \% \text{O}_2 = F(p\text{O}_{2\text{V}})$$

$$\text{C in vol. } \% \text{CO}_2 = f(p\text{CO}_{2\text{C}})$$

$$\text{C in vol. } \% \text{O}_2 = F(p\text{O}_{2\text{C}})$$

*Equations (5)* and *(6)* may then be expressed as follows:

$$p\text{CO}_{2\text{AL}} - p\text{CO}_{2\text{I}} = \text{R.Q.} \times (p\text{O}_{2\text{AL}} - p\text{O}_{2\text{I}_c}) \quad (7)$$

$$f(p\text{CO}_{2\text{V}}) - f(p\text{CO}_{2\text{C}}) = \text{R.Q.} \times F(p\text{O}_{2\text{C}}) - F(p\text{O}_{2\text{V}}) \quad (8)$$

Since complete equilibrium is assumed between the alveolar air and the blood leaving the alveolar capillaries,

$$p\text{CO}_{2\text{AL}} = p\text{CO}_{2\text{C}} \text{ and } p\text{O}_{2\text{AL}} = p\text{O}_{2\text{C}}$$

Substituting these values in *(8)* we have the system:

$$p\text{CO}_{2\text{AL}} - p\text{CO}_{2\text{I}} = \text{R.Q.} \times (p\text{O}_{2\text{I}_c} - p\text{O}_{2\text{AL}}) \quad (9)$$

$$f(p\text{CO}_{2\text{V}}) - f(p\text{CO}_{2\text{AL}}) = \text{R.Q.} \times F(p\text{O}_{2\text{AL}}) - F(p\text{O}_{2\text{V}})$$

When  $p\text{CO}_{2\text{V}}$ ,  $p\text{O}_{2\text{V}}$ ,  $p\text{CO}_{2\text{I}}$ ,  $p\text{O}_{2\text{I}}$  and R.Q. are known, the system *(9)* contains only 2 unknowns,  $p\text{CO}_{2\text{AL}}$  and  $p\text{O}_{2\text{AL}}$ , and may therefore be solved. There may be more than one solution for the two unknowns, but one and only one is possible in physical terms.

from figure 2, the composition of his mixed alveolar air was defined by some point along the line corresponding to  $R.Q. = 0.8$ , and from figure 3 the composition of the mixed blood leaving the alveolar capillaries was defined by some point along the line on this graph corresponding to  $R.Q. = 0.8$ . In figure 4

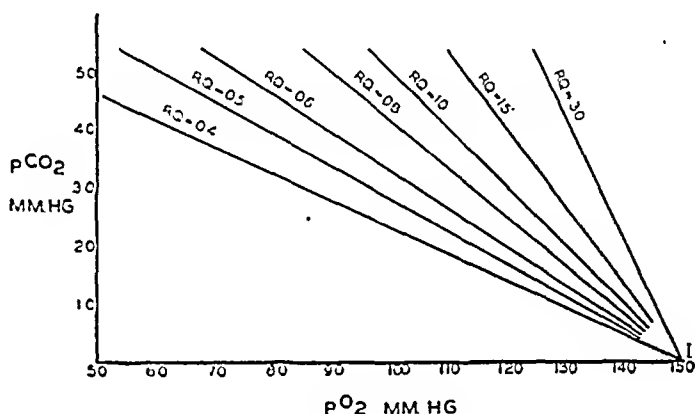


Fig. 2. ALVEOLAR AIR diagram after Fenn, Rahn and Otis.

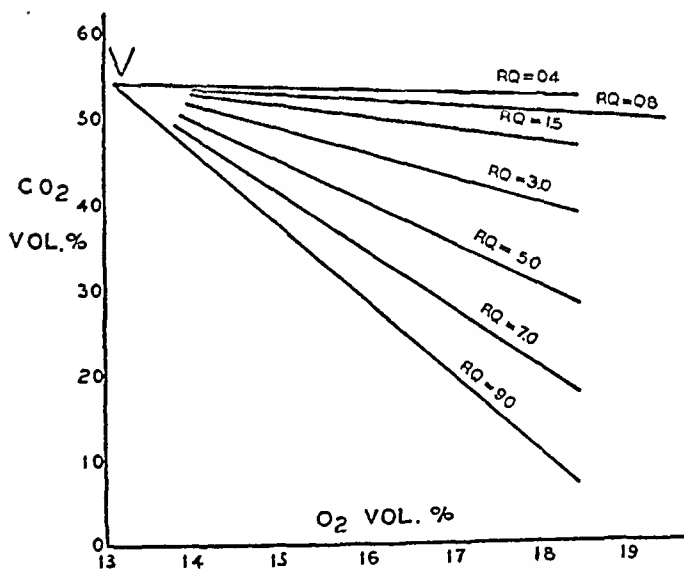


Fig. 3. ALVEOLAR capillary blood.

the blood  $R.Q.$  line has been replotted on the alveolar air diagram by converting from volumes per cent to partial pressure by reference to the appropriate blood-gas dissociation curves. The relationship between volumes per cent and partial pressure is not linear for either carbon dioxide or oxygen, so the blood  $R.Q.$  line in figure 4 is curved. The intersection of the two  $R.Q.$  lines

(fig. 4, X) is the point at which the blood and gas leaving the alveoli have the same  $p\text{CO}_2$  and  $p\text{O}_2$  at the R.Q. of the body as a whole. The point of intersection is thus the 'ideal' alveolar point. In figure 5 the blood R.Q. line has been plotted in terms of blood gas content, and X, transposed from figure 4, shows the respiratory gas content of 'ideal' capillary blood in equilibrium with

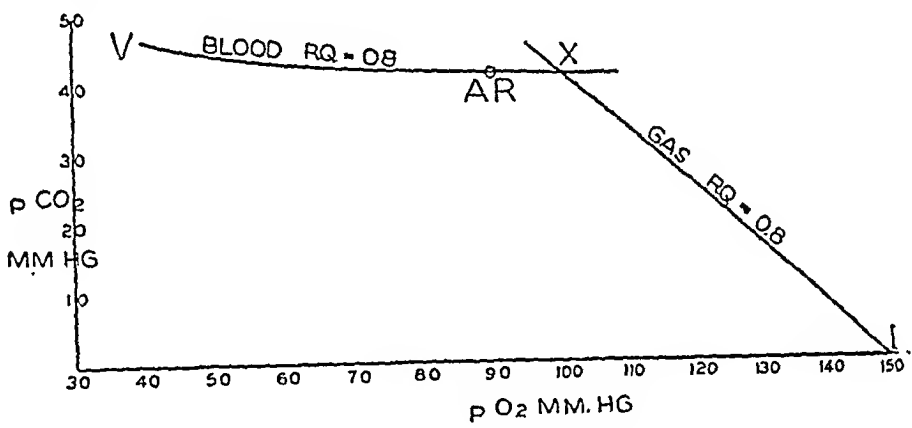


Fig. 4. X = 'IDEAL' alveolar point

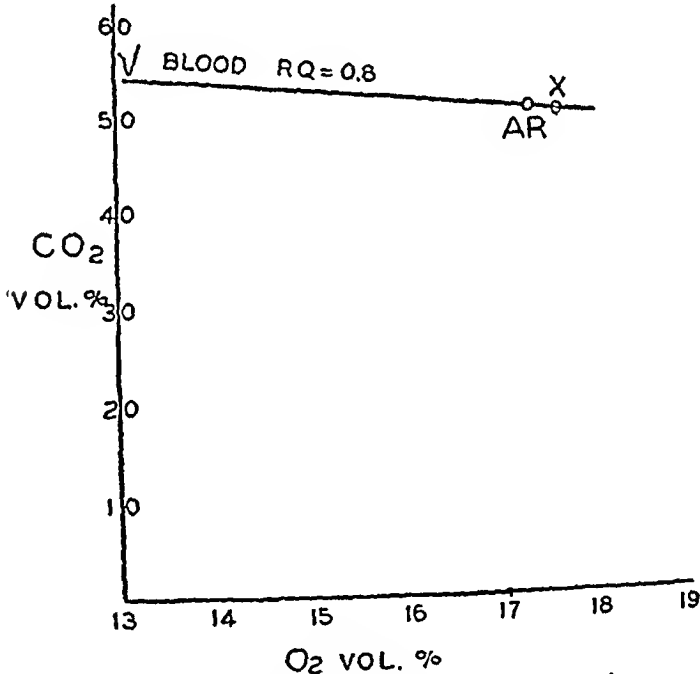


Fig. 5. X = 'IDEAL' alveolar capillary blood point

'ideal' alveolar air. Details of the construction of figures 4 and 5 are shown in the APPENDIX.

ALTERNATIVE METHOD FOR APPROXIMATING 'IDEAL' ALVEOLAR AIR

A simpler method for determining the 'ideal' point is based on the fact that the arterial  $p\text{CO}_2$  is essentially the same as the 'ideal' alveolar  $p\text{CO}_2$ . In figure 4 it can be seen that the blood R.Q. line, when plotted on the alveolar

air diagram, is very nearly horizontal in the region between the arterial blood point and the 'ideal' point. If it were truly horizontal, the arterial  $p\text{CO}_2$  would exactly equal the 'ideal' alveolar  $p\text{CO}_2$ . In normal individuals and in patients with moderate impairment of pulmonary function the approach to equality is within 1 mm. Hg and is close enough to justify the statement that arterial  $p\text{CO}_2$  is a good measure of 'ideal' alveolar  $p\text{CO}_2$ .

Alveolar  $p\text{O}_2$  may be calculated from the arterial  $p\text{CO}_2$  and the R.Q. This has been done by Rossier *et al.* (5), and independently by Riley, Lilienthal *et al.* (6). In effect this calculation determines the point on the gas R.Q. line where the  $p\text{CO}_2$  is that of the arterial blood. In figure 4, for example, arterial  $p\text{CO}_2 = 42$  mm. Hg; hence alveolar  $p\text{CO}_2$  would be considered 42 mm. Hg and alveolar  $p\text{O}_2$  would be calculated as 99.8 mm. Hg. This value for  $p\text{O}_2$  is virtually identical to that of the 'ideal' point where  $p\text{O}_2 = 100$  mm. Hg. The 'ideal'  $p\text{CO}_2$  is 41.8 mm. Hg as compared to the arterial  $p\text{CO}_2$  of 42 mm. Hg. It may thus be said that the calculated alveolar air values of Rossier *et al.* and of Riley and Lilienthal *et al.* are essentially the same as the 'ideal' alveolar air values except under special circumstances to be mentioned below.

The equation used by Rossier for calculating alveolar  $p\text{O}_2$  is very similar to a rearrangement of equation (4), with the gas concentrations expressed as partial pressures and with arterial  $p\text{CO}_2$  substituted for alveolar  $p\text{CO}_2$ :

$$\text{alv. } p\text{O}_2 = \frac{20.93}{100} (B - 49.5) - \frac{\text{art. } p\text{CO}_2}{\text{R.Q.}} \quad (10)$$

Rossier makes no correction for the change in volume between inspired air and alveolar air, and a slightly higher value is subtracted for water vapor tension than is customary in this country.

Riley, Lilienthal, *et al.* formerly used a modified form of equation (10) in which there was a partial correction for the change in volume between inspired air and alveolar air:

$$\text{alv. } p\text{O}_2 = \frac{20.93}{100} \times \frac{\text{exp. } \% \text{N}_2}{\text{insp. } \% \text{N}_2} (B - 47) - \frac{\text{art. } p\text{CO}_2}{\text{R.Q.}} \quad (11)$$

The theoretically correct equation, which has been derived by several authors (4, 7), is now being used in this laboratory.

$$\text{alv. } p\text{O}_2 = \text{insp. } p\text{O}_2 + \frac{\text{alv. } p\text{CO}_2 \times \text{insp. } \% \text{O}_2 \times (1 - \text{R.Q.})}{100 \times \text{R.Q.}} - \frac{\text{alv. } p\text{CO}_2}{\text{R.Q.}} \quad (12)$$

When arterial  $p\text{CO}_2$  is substituted for alveolar  $p\text{CO}_2$ , values for alveolar  $p\text{O}_2$  are obtained which are within 2 mm. Hg of those obtained using equation (11).

#### VARIATIONS IN DIFFERENT PARTS OF THE LUNGS

Since the 'ideal' alveolar air is accurately definable in physiological terms it provides a point of reference from which to analyze deviations from the

ideal. In the following section variations in the composition of alveolar air in different parts of the lungs will be investigated by the same graphic methods which led to the definition of the 'ideal' point itself, i.e. the intersections of blood and gas R.Q. lines of equal magnitude.

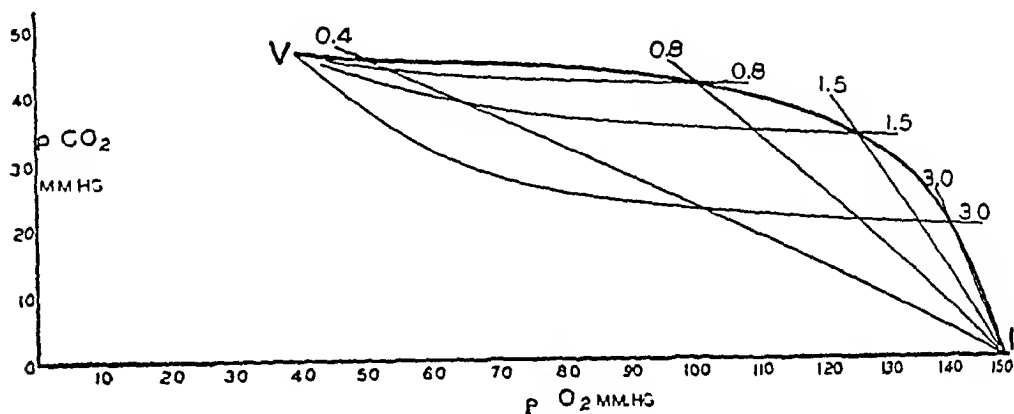


Fig. 6. Curve through all points at which blood R.Q. = gas R.Q.

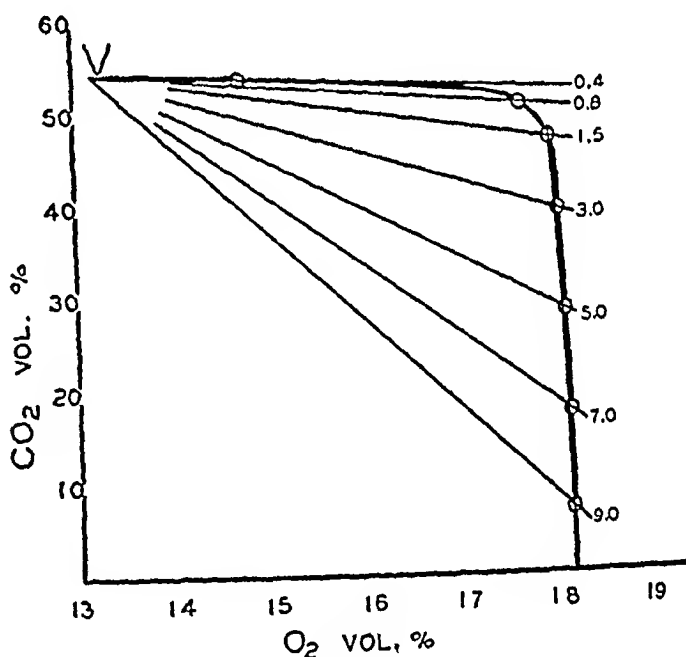


Fig. 7. COMPOSITION OF BLOOD LEAVING ALVEOLAR CAPILLARIES at all possible values of R.Q.

In figure 6 several blood and gas R.Q. lines are shown with a curve drawn through the points of intersection. Each point of intersection shows the respiratory gas tensions of the alveolar air and of the blood leaving the alveolar capillaries when a particular R.Q. obtains. The curve passes through the entire range of values for  $p\text{CO}_2$  and  $p\text{O}_2$ , corresponding to all possible values for R.Q. In figure 7 the curve of figure 6 has been redrawn in terms of blood

gas content. It shows the composition of blood leaving the alveolar capillaries at all possible values of R.Q.

In figure 8 the curve of figure 6 has been copied and 3 ventilation-perfusion ratios indicated. Points on the curve which are close to the mixed venous blood point represent alveoli which are well perfused with blood, but poorly ventilated. The mixed venous blood point itself corresponds to blood passing through non-ventilated alveoli or to venous admixture. Points near to the inspired air point represent alveoli which are well ventilated but poorly perfused. The inspired air point corresponds to alveolar air from completely non-perfused alveoli. Air passing in and out of such alveoli is unaltered and therefore comparable to dead space air.

In figure 9 the reasons for a high R.Q. in association with a high ventilation-perfusion ratio are shown graphically.  $\text{CO}_2$  and  $\text{O}_2$  contents for the mixed

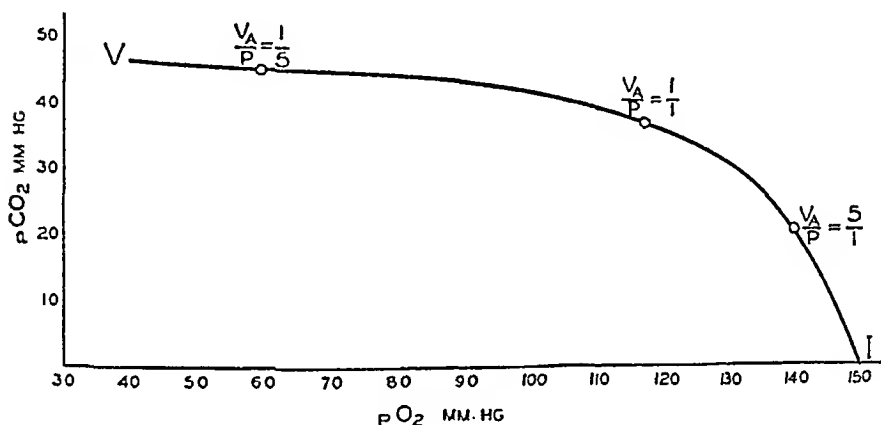


Fig. 8. CORRELATION BETWEEN VENTILATION-PERFUSION RATIOS and alveolar air tensions.

venous blood entering the alveoli (V), for the mixed arterial blood from the entire lung (AR), and for capillary blood leaving well ventilated but poorly perfused alveoli (C) are shown. The ratio in terms of volumes per cent of the  $\text{CO}_2$  V-AR difference to the  $\text{O}_2$  AR-V difference is to be contrasted with the ratio of the  $\text{CO}_2$  V-C difference to the  $\text{O}_2$  C-V difference for the alveoli with a high ventilation-perfusion ratio. The R.Q. is much higher in the latter because the segment of curve between AR and C is very steep in the case of  $\text{CO}_2$  and very flat in the case of  $\text{O}_2$ . The converse occurs when the ventilation-perfusion ratio is low, and the R.Q. of such areas falls below the over-all R.Q. of the lung as a whole.

The mixed blood leaving the alveolar capillaries is derived from alveoli with various R.Q.'s, and the mixed alveolar air also comes from alveoli with various R.Q.'s. Since in each case the R.Q. of the mixture is that of the body as a whole, the mixed blood leaving the alveolar capillaries (fig. 10, C) must



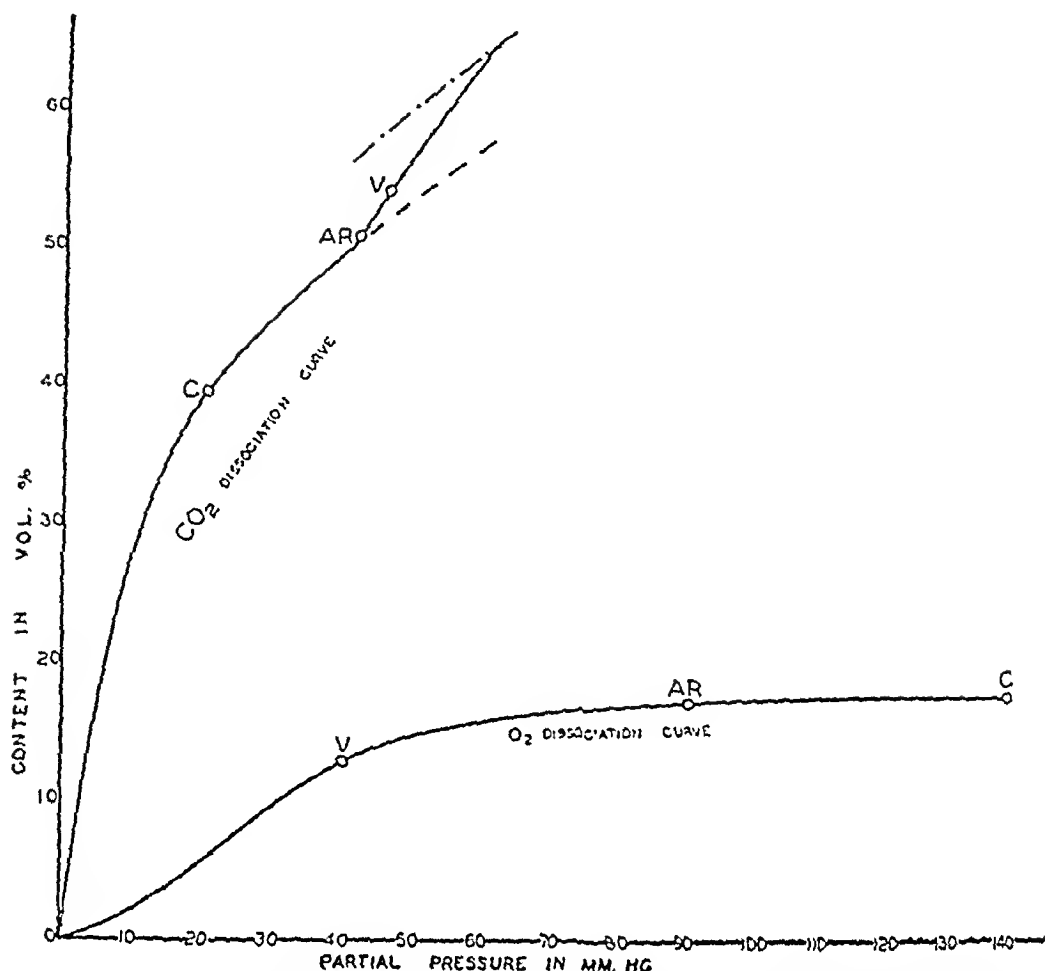


Fig. 9. PHYSIOLOGICAL OXYGEN AND CARBON DIOXIDE DISSOCIATION CURVES of blood plotted on the same scale. Ordinate = vol. %O<sub>2</sub> and vol. %CO<sub>2</sub> respectively; abscissa = pO<sub>2</sub> and pCO<sub>2</sub> respectively.

CO<sub>2</sub> dissociation curves = --- fully oxygenated blood; - - - - - fully reduced blood; V = mixed venous blood; AR = mixed arterial blood; C = blood leaving an alveolus which is well ventilated but poorly perfused.

$$R.Q. \text{ for lung as a whole} = \frac{V - A \text{ in vol. \%CO}_2}{A - V \text{ in vol. \%O}_2} = \frac{54.1 - 50.75}{17.3 - 13.1} = 0.8$$

$$V_A/P \text{ for lung as a whole} = \frac{V - A \text{ in vol. \%CO}_2}{AL - I \text{ in \%CO}_2} = \frac{54.1 - 50.75}{5.85 - 0} = 0.57$$

where

$$AL \text{ in \%CO}_2 = \frac{\text{art. pCO}_2}{B - 47} \times 100 = \frac{42}{718} \times 100 = 5.85$$

$$R.Q. \text{ for hyperventilated alveoli} = \frac{V - C \text{ in vol. \%CO}_2}{C - V \text{ in vol. \%O}_2} = \frac{54.1 - 39.5}{17.9 - 13.1} = 3.0$$

$$V_A/P \text{ for hyperventilated alveoli} = \frac{V - C \text{ in vol. \%CO}_2}{AL - I \text{ in \%CO}_2} = \frac{54.1 - 39.5}{2.9 - 0} = 5.0$$

where

$$AL \text{ in \%CO}_2 = \frac{\text{cap. pCO}_2}{B - 47} \times 100 = \frac{21}{718} \times 100 = 2.9.$$

lie along the blood R.Q. line for R.Q. = 0.8, and the mixed alveolar air (fig. 10, AL) must lie along the gas R.Q. line for R.Q. = 0.8. The mixed capillary

blood is influenced more by alveoli lying to the left of the 'ideal' point than by those lying to the right, since perfusion is large in proportion to ventilation in these areas (low  $V_a/P$  ratio). The mixed alveolar air is influenced more by

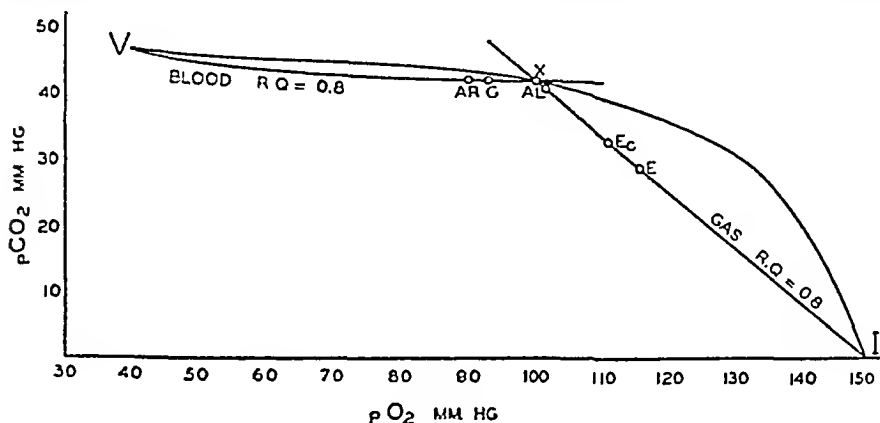


Fig. 10. EFFECTS UPON BLOOD AND GAS of variations in ventilation-perfusion ratio. X = "ideal" alveolar point; C = mixed blood leaving the alveolar capillaries; AR = mixed arterial blood; AL = mixed alveolar air leaving the alveoli, i.e. alveolar component of the expired air; E = expired air;  $E_c$  = expired air corrected for the effect of apparatus dead space; V = mixed venous blood; I = inspired air.

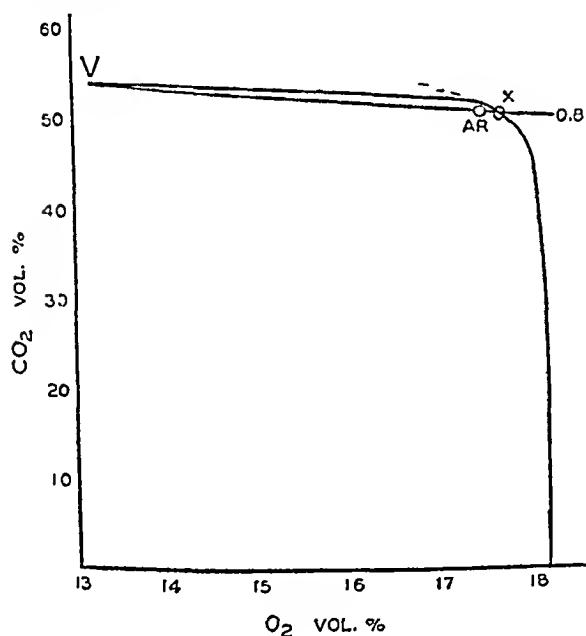


Fig. 11. EFFECT upon blood of variations in ventilation-perfusion ratio.

alveoli lying to the right of the 'ideal' point (high  $V_a/P$  ratio) than by those lying to the left, since ventilation is large in proportion to perfusion. Neither the mixed capillary blood nor the mixed alveolar air can be determined accu-

rately, but approximate values are plotted in figure 10 for the sake of the theoretical discussion. In figure 11 the effect upon the mixed arterial blood of variations in ventilation-perfusion ratio is plotted in terms of volumes per cent.

#### QUANTITATIVE ESTIMATION OF VARIATIONS IN VENTILATION-PERFUSION RATIO

Quantitative estimation of variations in ventilation-perfusion ratio depends upon the magnitude of the difference between the 'ideal' alveolar air and the mixed alveolar air and mixed capillary blood, respectively. If there were no such variations the partial pressures of the mixed alveolar air and the mixed alveolar capillary blood would be identical to each other and to the 'ideal' alveolar air. As shown above, however, ventilation of poorly perfused alveoli causes the composition of the mixed alveolar air to diverge from the 'ideal' along the gas R.Q. line in the direction of the inspired air. Perfusion of poorly ventilated alveoli causes the composition of the mixed capillary blood to diverge from the 'ideal' along the blood R.Q. line in the direction of the mixed venous blood. Although in each case these are the resultant effects of innumerable alveoli with different ventilation-perfusion ratios, it is nevertheless possible to describe the effect upon the mixed alveolar air as comparable to that which would result from the admixture of a certain proportion of inspired air to the 'ideal' alveolar air. The effect upon the mixed capillary blood can likewise be described as comparable to that which would result from the admixture of a certain proportion of mixed venous blood to 'ideal' capillary blood. It is therefore theoretically possible to quantitate the effects of variations in ventilation-perfusion ratio in terms of inspired air, or dead space air, admixture and venous admixture.

Unfortunately, since mixed alveolar air and mixed capillary blood cannot be determined with accuracy, the contributions to dead space admixture and venous admixture which result from variations in ventilation-perfusion ratio cannot be separated from the contributions resulting from anatomical dead space and true venous admixture. It is therefore necessary to measure the combined effects of both contributions and to expand the usual concepts of dead space and venous admixture. Dead space is considered to include not only the anatomical dead space but also a contribution from alveoli with a high ventilation-perfusion ratio. Venous admixture includes not only blood from the bronchial veins, Thebesian veins, shunts, etc., but also a contribution from alveoli with a low ventilation-perfusion ratio.

There are several corollaries to these concepts of dead space and venous admixture. The calculated alveolar ventilation, which is the difference between total ventilation and dead space ventilation, is reduced by the same amount that dead space ventilation is increased. The calculated alveolar

perfusion with blood is reduced by the amount by which venous admixture is increased. All alveoli are arbitrarily considered in 3 categories: those with an 'ideal' ventilation-perfusion ratio; those which are ventilated but not perfused; and those which are perfused but not ventilated.

*Dead Space.* The determination of dead space requires the following data: alveolar  $p\text{CO}_2$ , expired air  $p\text{CO}_2$ , inspired air  $p\text{CO}_2$ , tidal air volume and the volume of dead space in the apparatus. The Bohr equation may then be applied:

$$\text{Dead space} = \frac{(X - E)}{(X - I)} \times \text{tidal air} - \text{dead space of apparatus}$$

$$X = \text{'Ideal' alveolar } p\text{CO}_2 = \text{arterial } p\text{CO}_2. \quad (13)$$

TABLE 1. VENTILATION-PERFUSION RELATIONSHIPS IN 8 NORMAL MALE PHYSICIANS

SUBJECT	BAROMETRIC PRESSURE	'IDEAL' ALVEOLAR		ARTERIAL		ALVEOLAR- ARTERIAL GRADIENT $p\text{O}_2$	DEAD SPACE TIDAL AIR	VENOUS ADMIXTURE CARDIAC OUTPUT
		$p\text{CO}_2$	$p\text{O}_2$	$p\text{CO}_2$	$p\text{O}_2$			
	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	%	%
R. L. R.....	765	42	100	42	90	10	21	4.8
J. B. J.....	763	38	102	38	96	6	25	2.6
J. D.....	761	37	104	37	91	13	13	6.2
R. A.....	767	37	111	37	102	9	19	3.7
J. F.....	762	40	102	40	93	9	19	3.8
W. J. L.....	763	36	107	36	95	12	12	5.8
R. N.....	758	43	94	43	91	3	21	1.7
K. B.....	762	36	110	36	99	11	29	4.6
Average.....		38.6	103.7	38.6	94.6	9.1	19.9	4.2

Subjects at rest in the supine position. Ages ranged from 28 to 40 years.

This expression may be divided by the tidal air volume to determine the ratio of dead space to tidal air.

In order to use the calculated dead space as a means of estimating the physiological importance of alveoli in which the ventilation-perfusion ratio is higher than the 'ideal,' one must compare the patient's dead space to that of a normal individual. Normal values calculated in this way vary considerably in absolute terms but when expressed as the ratio of dead space to tidal air they become fairly constant. The ratio can be varied by altering the respiratory pattern, but when the individual responds to normal physiological drives the normal ratio of dead space to tidal air falls below 30 per cent at rest. During exercise the ratio either stays the same or falls. When the dead space volume exceeds 30 per cent of the tidal air volume it may be concluded that a significant proportion of alveoli have a ventilation-perfusion ratio which is higher than the 'ideal' (table 1).

The significance of the dead space value differs when different technics are used for making the determination. In a recent report by Fowler (8) "respiratory dead space was measured by simultaneous and continuous measurement of volume flow and  $N_2$  content (Lilly-Hervey nitrogen meter) of gas expired following inhalation of 99.6 per cent  $O_2$ ." Dead space values were said to be affected by: 1) anatomical volume of the bronchial tree; 2) gas diffusion between terminal bronchioles and alveolar spaces; and 3) uniformity of gas mixing throughout the lung. In Birath's method (9), which involves the intrapulmonary mixing of the inert gas hydrogen, the calculated value for dead space is also affected by the efficiency with which the gas is distributed throughout the lungs. Haldane's method (10), in which alveolar  $CO_2$  is used, is affected by ventilation-perfusion relationships, but because of the technic used for sampling alveolar air the results are ambiguous during exercise or in patients with pulmonary disease. The introduction of the Sonne-Nielsen alveolar sampling technic (11) is an improvement but does not settle the question as to the representative nature of the alveolar sample. The use of arterial  $pCO_2$  in the dead space determination eliminates ambiguity regarding the alveolar sample. The ratio of dead space to tidal air then becomes a value which can be used in the quantitative evaluation of areas of the lung having a high ventilation-perfusion ratio.

The relationship between dead space and tidal air can be visualized graphically, provided a correction is made for the effect of apparatus dead space upon the composition of the expired air. In figure 10,  $E_c$  represents the composition which the expired air would have had if there had been no apparatus dead space. The ratio of dead space to tidal air corresponds to the ratio of  $X-E_c$  to  $X-I$ .

The ratio of alveolar ventilation to total ventilation is 1 minus the ratio of dead space to tidal air. The minute volume of alveolar ventilation can be calculated either from this relationship or from the basic equation:

$$\text{alveolar ventilation} = \frac{CO_2 \text{ output} \times 100}{\text{'ideal' alveolar } \%CO_2} \quad (14)$$

*Venous Admixture.* The ratio of venous admixture to total blood flow, i.e. cardiac output, can be calculated in a manner analogous to the calculation of the dead space ratio:

$$\frac{V.A.}{C.O.} = \frac{X - AR, \text{ in vol. } \%O_2}{X - V, \text{ in vol. } \%O_2} \quad (15)$$

The term venous admixture is here used in the expanded sense and includes contributions of blood from poorly ventilated alveoli. The relationships described by equation (15) can be visualized in figure 11.

The calculation of venous admixture requires that the 'ideal' alveolar-

arterial  $O_2$  gradient be expressed in terms of volume per cent. Since the arterial blood normally falls on the upper flat portion of the oxygen dissociation curve, where a very small error in the oxygen content causes a significant error in  $pO_2$ , it is preferable to use the directly determined arterial  $pO_2$  as the starting point in calculating venous admixture. The 'ideal' alveolar-arterial  $pO_2$  gradient can then be transposed into volumes per cent by reference to a standard oxyhemoglobin dissociation curve.

The ratio of alveolar perfusion with blood to total blood flow is 1 minus the ratio of venous admixture to total blood flow. Alveolar perfusion is readily calculated in absolute terms when the cardiac output is known.

When mixed venous blood is not known, 2 alternative procedures may be adopted. If the subject is in the resting state and is not in cardiac failure, an arterio-venous difference of 4.3 vols. per cent oxygen may be assumed (12) and the percentage of venous admixture calculated as above. The error in

TABLE 2. VENTILATION-PERFUSION RELATIONSHIPS IN 6 INDIVIDUALS WITH EMPHYSEMA

SUBJECT	BAROMETRIC PRESSURE	'IDEAL' ALVEOLAR		ARTERIAL		ALVEOLAR- ARTERIAL GRADIENT $pO_2$	DEAD SPACE TIDAL AIR	VENOUS ADMIXTURE CARDIAC OUTPUT
		$pCO_2$	$pO_2$	$pCO_2$	$pO_2$			
	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	%	%
M. F.....	761	38	104	38	92	12	23	7.6
T. M.....	754	49	89	49	70	19	48	17.5
L. L.....	766	35	113	35	66	47	47	22.3
L. P.....	766	55	79	55	50	29	44	34.6
H. W.....	769	54	84	54	49	35	52	40.8
A. D.....	762	56	81	56	37	44	35	54.0

Subjects at rest in the supine position. Corrections made when necessary for the effect of a diffusion gradient.

this procedure is ordinarily not great because the numerator in equation (15), which is not affected by the assumed value for mixed venous blood, is much more critical than the denominator.

The other alternative, when mixed venous blood is not known, is to estimate the amount of venous admixture on the basis of the 'ideal' alveolar-arterial  $pO_2$  gradient alone. When the subject is at rest and breathing room air, a gradient in excess of 12 mm. Hg may be considered abnormally large. This datum must be interpreted with discretion, however, since the significance of the 'ideal' alveolar-arterial  $pO_2$  gradient is affected both by the level of oxygenation of the arterial blood and by the arterio-venous difference.

#### EXPERIMENTAL FINDINGS

Average normal values of 'ideal' alveolar air have previously been reported under the name of 'effective' alveolar air (6), and the corresponding alveolar-arterial  $pO_2$  gradients were also presented (13). In table 1 a more

complete analysis of ventilation-perfusion relationships in 8 normal male physicians is presented. The average values are almost identical with those previously reported.

The upper limits of normal for subjects resting in the supine position breathing ambient air have been tentatively set at 12 or 13 mm. Hg for alveolar-arterial  $pO_2$  gradient, 30 per cent for the ratio of dead space to tidal air, and 7 per cent for the ratio of venous admixture to cardiac output.

In table 2 the findings in 6 individuals with various types and degrees of pulmonary emphysema are recorded. In the second case (*T. M.*) the inefficiency is largely ventilatory as indicated by a high ratio of dead space to tidal air (48%) and only a moderately high ratio of venous admixture to cardiac output (17.5%). In the last case (*A. D.*) the opposite situation obtains.

The ratio of effective tidal air to tidal air, or of effective alveolar ventilation to total ventilation, is, in percent, 100 minus the ratio of dead space to tidal air. The ratio of effective pulmonary blood flow to total pulmonary blood flow, or cardiac output, is 100 minus the ratio of venous admixture to cardiac output.

#### DISCUSSION

In a previous analysis of the alveolar-arterial gradient the theoretical necessity for the alveolar air and alveolar capillary blood to approach equilibrium more closely at high levels of oxygenation than at low levels was discussed (13). This phenomenon was suggested many years ago by Barcroft and has been elaborated upon by recent authors (14, 15). It is not to be inferred that the mean  $pO_2$  gradient between alveolar air and alveolar capillary blood is necessarily different at different levels of oxygenation but simply that the final gradient as the blood leaves the alveolar capillary is different. This final gradient, which we shall call the diffusion gradient, differs because of the shape of the oxyhemoglobin dissociation curve. There are theoretical reasons for believing that the diffusion gradient is but a fraction of 1 mm. Hg in normal resting individuals breathing room air at sea level (13, 15), while the gradient increases to as much as 9 mm. Hg when the arterial oxygen saturation is reduced to 70 per cent by breathing a low oxygen gas mixture (13, 15).

In the analysis of venous admixture above it was assumed, as it has been throughout this paper, that no diffusion gradient existed, i.e. that perfect equilibrium was reached between the alveolar gases and the blood leaving the alveolar capillaries. This is a valid assumption, for practical purposes, in resting subjects whose arterial oxygen saturation is 96 per cent or higher during room air breathing. At such high levels of oxygenation, therefore, the  $pO_2$  gradient between 'ideal' alveolar air and arterial blood is predominantly the resultant effect of venous admixture and perfusion of poorly ventilated alveoli. At an arterial oxygen saturation of 70 per cent not only does the diffusion

gradient increase, but the venous admixture gradient decreases. In normal individuals the venous admixture  $pO_2$  gradient is believed on theoretical grounds to decrease to a fraction of 1 mm. Hg so that the total  $pO_2$  gradient between 'ideal' alveolar air and arterial blood is predominantly the effect of failure to reach equilibrium, i.e. diffusion (13, 14, 15). Recent unpublished studies indicate that the 'ideal' alveolar-arterial  $pO_2$  gradient can be quantitatively apportioned between diffusion (the membrane component) and venous admixture (the venous admixture component) provided the alveolar-arterial gradient is determined at two different levels of oxygenation, with the subject in the same metabolic state.

The  $pCO_2$  gradient between alveolar air and the blood leaving the alveolar capillaries remains negligible at low levels of oxygenation. Thus, in the absence of a large shunt, the arterial  $pCO_2$  remains a good measure of alveolar  $pCO_2$ , and the 'ideal' alveolar  $pO_2$  can be calculated in the usual way using *equation* (12). The graphic method for determining 'ideal' alveolar  $pO_2$  cannot be applied in the presence of a  $pO_2$  diffusion gradient since this method is based upon the identity of alveolar  $pO_2$  and the  $pO_2$  of the blood leaving the individual alveolar capillaries. The graphic method therefore cannot be used during low oxygen breathing.

In the system of analysis of ventilation-perfusion relationships which has been presented it has been assumed that the blood R.Q., the alveolar air R.Q. and the expired air R.Q. are identical (1, 20, 21). A factor which would invalidate this assumption would be the exchange of significant quantities of oxygen or carbon dioxide through the walls of the larger airways. While some such exchange may possibly take place (16) it is undoubtedly small in amount and therefore not an important source of error. Another cause for discrepancy between the alveolar R.Q. and the expired air R.Q. would be anything causing an unsteady state, such as recent changes in activity or in the composition of the inspired air. Errors from such causes are minimized in practice by requiring the subject to maintain as constant a state as possible prior to and during the collection of samples. Exercise is performed on a stationary bicycle at a steady level for 7 minutes before sampling is begun, and subjects are required to breathe high or low oxygen mixtures for 10 minutes before sampling. These leveling off periods are not adequate to produce a completely steady state, but the consistency and reproducibility of results suggest that errors from this cause are not large. Strictly speaking, a steady state can never be achieved because of the cyclic nature of the ventilatory and circulatory processes. It is probable that moment to moment variations are responsible for some of the variations in ventilation-perfusion ratio for which there is evidence in normal individuals.

Rossier has pointed out that a large shunt may lead to a significant difference between arterial and alveolar  $pCO_2$ , and we have observed a difference



as great as 3 mm. Hg in patients with severe degrees of emphysema. Under these circumstances the 'ideal' alveolar  $p\text{CO}_2$  can be accurately determined by the graphic method. On theoretical grounds it would seem that impaired diffusion across the alveolar membrane will not lead to a significant  $p\text{CO}_2$  gradient until the  $p\text{O}_2$  gradient has become so great as to be incompatible with life. Impaired diffusion of  $\text{O}_2$  therefore does not invalidate the use of arterial  $p\text{CO}_2$  as a measure of 'ideal' alveolar  $p\text{CO}_2$ .

There is no apparent reason why the 'ideal' alveolar air cannot be calculated by the graphic method even in the presence of congenital cardiac disease with large vascular shunts. One point and slope are all that is required to draw the blood and gas R.Q. lines, and in each case the R.Q., determined from the expired air, provides the slope. The arterial blood provides a point on the blood R.Q. line and inspired air provides a point on the gas R.Q. line. The point of intersection can be found graphically. Once the 'ideal' alveolar point is established, the ratio of dead space to tidal air can be calculated, providing evidence related to ventilation-perfusion relationships within the lungs in patients with congenital heart disease. The ratio of venous admixture to cardiac output will include the effects of both intrapulmonary shunt and right to left intracardiac shunts.

Technical errors must be carefully minimized in the performance of the direct blood gas tension technic (17). It is helpful to calculate the arterial  $p\text{CO}_2$  from the Henderson-Hasselbalch relationships in order to check the direct method. The arterial  $p\text{O}_2$  determination can be compared with the oxygen saturation if the  $p\text{H}$  is known. The apparatus dead space, which includes the entire volume between the subject's mouth and both respiratory valves, must be reduced to a minimum and accurately measured in order to permit accurate physiological dead space determinations.

It has been observed consistently that the ratio of dead space to tidal air remains fairly constant in a given individual at rest, during moderate exercise, and during high and low oxygen breathing. This is true in both health and disease. The finding is constant enough to help in deciding whether an experiment is technically satisfactory. Furthermore, venous admixture and dead space are affected in opposite ways by an error in arterial  $p\text{CO}_2$ , so that inaccuracies may often be detected by examining these relationships.

One of the factors determining the magnitude of the venous admixture effect resulting from perfusion of poorly ventilated alveoli is the change in slope of the oxygen dissociation curve in the physiological range. When the subject breathes ambient air or air with a  $p\text{O}_2$  in the vicinity of 150 mm. Hg, the blood in the alveolar capillaries covers a range of the oxygen dissociation curve which extends from the steepest portion to the very flat upper portion. This maximal change in slope provides conditions which cause blood from poorly ventilated alveoli to contribute maximally to the venous admixture

effect. If the same subject breathes a low oxygen mixture, the venous admixture effect resulting from perfusion of poorly ventilated alveoli is much reduced because the physiological range of the oxygen dissociation curve is limited to the steep portion where the change in slope is relatively slight. Finally, if the same subject breathes pure oxygen, the venous admixture effect from poorly ventilated areas is eliminated, in this case because the curve of intersections of the blood and gas R.Q. lines becomes a straight line. Under these conditions venous admixture measures only true shunt. Analysis of ventilation-perfusion relationships must be done where the resulting venous admixture effect is maximal and must therefore be done with the subject breathing ambient air or air in this general range.

Several methods have been proposed by which the distribution of the tidal air throughout the lungs can be evaluated (22, 23, 9, 24). The study of the ventilation-perfusion relationships differs from these in that the distribution of the tidal air is considered only in relation to the distribution of the alveolar capillary blood. If the distribution of the tidal air and the ventilation-perfusion relationships are evaluated independently it would seem possible to learn something about the distribution of alveolar capillary blood as an independent phenomenon. Furthermore, since the use of high concentrations of oxygen tends to reduce the apparent venous admixture resulting from perfusion of poorly ventilated alveoli, it may be possible to differentiate in part between true shunt and apparent venous admixture (25, 26). Such combinations of studies would lead to more precise understanding of ventilation and perfusion both as independent and as related phenomena.

## APPENDIX

### DETERMINATION OF 'IDEAL' ALVEOLAR AIR

The graphic determination of 'ideal' alveolar point requires the following data. For purposes of illustration values obtained on a normal subject will be used.

Subject: *R. L. R.*; barometric pressure: 765 mm. Hg

Blood:

	<i>Arterial</i>		<i>Mixed venous</i>
pCO <sub>2</sub>	42	mm. Hg	
pO <sub>2</sub>	90	mm. Hg	
CO <sub>2</sub> content	50.75	vol. %	
O <sub>2</sub> content	O <sub>2</sub> Hb = 17.1		O <sub>2</sub> Hb = 13.1
	Dissolved = .3		Dissolved = .1
	Total 17.4	vol. %	Total = 13.2
O <sub>2</sub> capacity	O <sub>2</sub> Hb = 17.9		O <sub>2</sub> Hb = 17.9
	Dissolved = .5		Dissolved = .5
	Total = 18.4	vol. %	Total = 18.5
O <sub>2</sub> Hb saturation	95.5	%	
Expired air:			
CO <sub>2</sub> .....			4.05 %; 29.1 mm. Hg
O <sub>2</sub> .....			16.10 %

N <sub>2</sub> .....	79.85 %
Ventilation.....	6.18 l/min. BTPS; 5.14 l/min. STPD
Tidal air.....	672 ml/breath BTPS
Respiratory rate.....	9.2 breaths/min.

*Plotting gas R.Q. line, using  $p\text{CO}_2$  and  $p\text{O}_2$  as coordinates.* The moist inspired air point is calculated from the equation  $\text{insp. } p\text{O}_2 = \frac{20.93}{100} (B - 47)$ . A value for alveolar  $p\text{CO}_2$ , such as 40 mm. Hg, is assumed, and the corresponding value for alveolar  $p\text{O}_2$  is calculated using equation (12). A straight line is drawn through the inspired air point ( $p\text{O}_2 = 150$  mm. Hg;  $p\text{CO}_2 = 0$ ) and the assumed alveolar point ( $p\text{CO}_2 = 40$  mm. Hg;  $p\text{O}_2 = 102$  mm. Hg) (Figure 4, gas R.Q. line).

*Plotting the blood R.Q. line, using vol. %  $\text{CO}_2$  and  $\text{O}_2$  as coordinates.* The blood R.Q. line passes through both the mixed venous blood point and the arterial blood point. In subjects whose mixed venous blood and arterial blood have both been directly sampled, these two points can be plotted and a straight line drawn through them. However, since the R.Q. determines the slope of this line, one directly determined point and the R.Q. suffice for drawing the line. Ordinarily the arterial blood point is plotted as in figure 5;

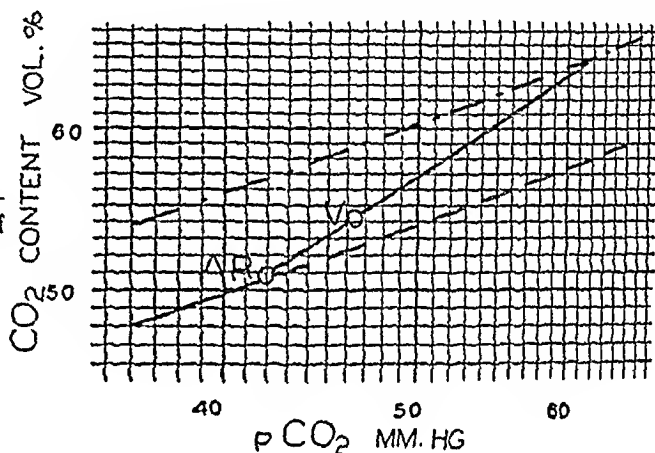


Fig. 12. PHYSIOLOGICAL carbon dioxide dissociation curve of R.L.R. plotted on log paper.

a second point is located by assuming a  $\text{CO}_2$  arterio-venous difference, such as 4.0 vol. %, and counting off the corresponding  $\text{O}_2$  arterio-venous difference as indicated by the R.Q.  $\left(\frac{4.0}{0.8} \approx 5.0 \text{ vol. \% O}_2 \text{ A - V difference}\right)$ . A straight line through the assumed point ( $\text{CO}_2 = 54.75 \text{ vol. \%}$ ;  $\text{O}_2 = 12.4 \text{ vol. \%}$ ) and the arterial blood point is the blood R.Q. line. It passes through the mixed venous blood point, although the exact location of the latter will not be known unless it has been determined by other technics.

*Transposing the blood R.Q. line to the alveolar air diagram.* Transposition of the blood R.Q. line from the volumes per cent plot (fig. 5) to the partial pressure plot (fig. 4) requires that the physiological carbon dioxide and oxygen dissociation curves for the individual under consideration be constructed. Details of the methods for accomplishing this have been described elsewhere (18, 19), so only the steps involved will be mentioned here.

The physiological  $\text{CO}_2$  dissociation curve is plotted on log log graph paper with vol. %  $\text{CO}_2$  laid off along the vertical axis and  $p\text{CO}_2$  along the horizontal (fig. 12). Knowledge of the mixed venous blood is not needed and the procedure will therefore be described as if this value were not known. The arterial blood point is plotted. The difference in  $\text{CO}_2$  content between completely reduced and fully oxygenated blood is determined (6.2 vol.

% and the  $\text{CO}_2$  content of fully oxygenated blood calculated (50.5 vol. %  $\text{CO}_2$  at  $\text{pCO}_2 = 42$  mm. Hg), taking into account the oxygen unsaturation of the arterial blood. The  $\text{CO}_2$  dissociation curve for fully oxygenated blood is drawn through this point, after determining the slope on the basis of the  $\text{O}_2$  Hb capacity. A dissociation curve for unsaturated blood is then drawn parallel to the curve for oxygenated blood. The carbon dioxide content corresponding to zero oxygen content is determined (64.9 vol. %), taking into consideration the R.Q. The point on the dissociation curve for unsaturated blood is found where the  $\text{CO}_2$  content = 64.9. A straight line drawn through this point and the arterial blood point is the physiological  $\text{CO}_2$  dissociation curve (fig. 12). It intersects the curve for fully oxygenated blood at  $\text{pCO}_2 = 41$  mm. Hg. The physiological curve is discontinuous at this point, becoming the same as the fully oxygenated curve at  $\text{pCO}_2$  values below 41 mm. Hg

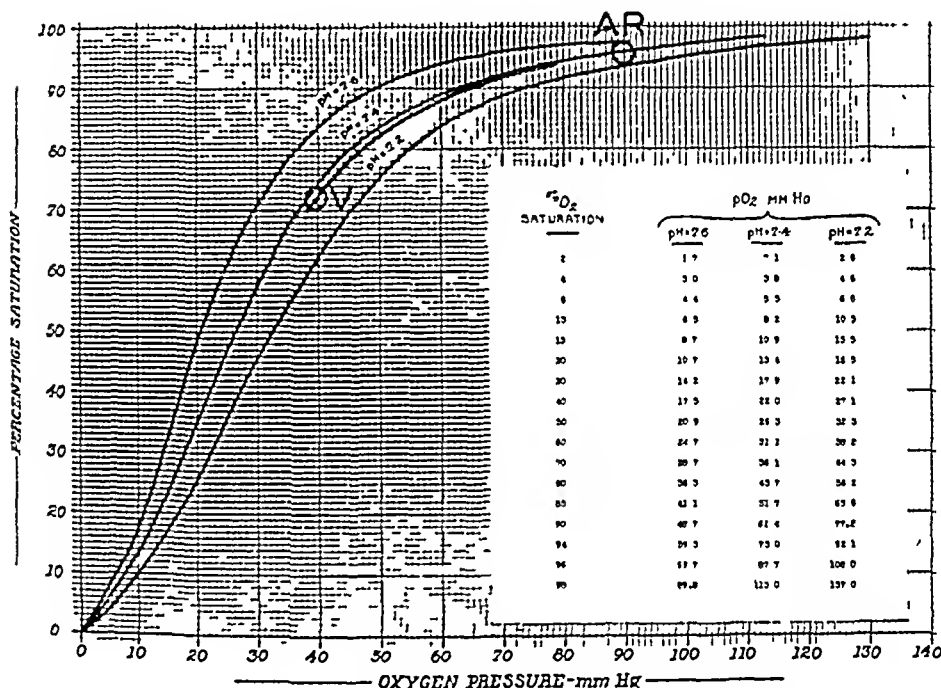


Fig 13 PHYSIOLOGICAL oxygen dissociation curve of RLR Standard curves from *Hand book of Respiratory Data in Aviation Medicine*

To construct the physiological oxygen dissociation curve the arterial blood point is plotted on a standard oxygen dissociation curve (linear coordinates) on the basis of directly determined  $\text{pO}_2$  and  $\text{O}_2$  Hb saturation values (fig 13). Since the  $\text{pH}$  of mixed venous blood is 0.02 or 0.03  $\text{pH}$  units lower than that of the arterial blood, the venous blood point is displaced about 2 mm Hg to the right of the dissociation curve which passes through the arterial blood point. The physiological oxygen dissociation curve can be drawn with sufficient accuracy by eye between the arterial and mixed venous blood points, almost paralleling the standard curve for constant  $\text{pH}$ . This procedure is permissible because the effect of the difference in  $\text{pH}$  between arterial and mixed venous blood is small.

When the carbon dioxide and oxygen dissociation curves have been constructed, the necessary relationships are available for expressing the blood R.Q. line in terms of  $\text{pCO}_2$

and  $pO_2$ . In table 3 the data used in transposing this line from figure 5 to figure 4 are presented. Oxygen content values from figure 5 are first divided by the oxygen capacity and expressed as per cent saturation. Then the corresponding  $pO_2$  values are read off from the physiological oxygen dissociation curve (fig. 13). Values of  $CO_2$  content from figure 5 are expressed in terms of  $pCO_2$  by reference to the physiological  $CO_2$  dissociation curve (fig. 12). The  $pO_2$  and  $pCO_2$  values are plotted in figure 4. The 'ideal' point, identified by the intersection of the blood and gas R.Q. lines, has a  $pCO_2$  of 41.8 mm. Hg and a  $pO_2$  of 100 mm. Hg.

TABLE 3. SUBJECT R. L. R. ( $O_2Hb$  CAPACITY = 17.9 VOL. %)

CARBON DIOXIDE		OXYGEN				
vol. %	mm. Hg	Content in vol %		Total	% Saturation	mm. Hg
		$O_2Hb$	Dissolved			
V = 54.1	46.5	13.1	.1	13.2	73.0	40
53.4	45.5	14.0	.1	14.1	78.1	44
51.9	43.4	15.9	.2	16.1	88.9	59
AR = 50.75	42.0	17.1	.3	17.4	95.6	90
X = 50.60	41.7	17.3	.3	17.6	96.7	100
50.5	41.6	17.5	.3	17.8	97.9	108

### SUMMARY

The partial pressure of oxygen in the alveolar air may vary widely in different parts of the lungs in patients with pulmonary disease. The composition which the alveolar air would have if it were homogeneous throughout the lungs can be determined precisely by solving the blood and gas R.Q. equations, assuming that there is equilibrium between the alveolar air and the blood leaving the alveolar capillaries. Alveolar air of the one and only composition which satisfies these equations is called the 'ideal' alveolar air.

Variations in the composition of alveolar air in different parts of the lungs occur primarily because of variations in ventilation-perfusion ratio. These relationships can be analyzed, using the 'ideal' alveolar air concept. Physiological dead space, when calculated using the 'ideal' alveolar air, includes a contribution from alveoli with a high ventilation-perfusion ratio. A ratio of dead space to tidal air in excess of 30 per cent indicates that a significant proportion of alveoli are well ventilated but poorly perfused. Venous admixture, when calculated using the 'ideal' value for blood leaving the alveolar capillaries, includes a contribution from alveoli with a low ventilation-perfusion ratio. A ratio of venous admixture to cardiac output in excess of 7 per cent indicates that a significant proportion of alveoli are well perfused but poorly ventilated. Analysis of ventilation-perfusion relationships must be done in the normal range of oxygenation, since breathing either a low oxygen mixture or a very high oxygen mixture minimizes the effects under consideration.

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## *Electrolyte Changes with Chronic Passive Hyperventilation in Man<sup>1</sup>*

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**A**LTHOUGH THE EFFECTS of chronic hyperventilation in the presence of low oxygen tension have been studied exhaustively by many investigators, a search of the literature fails to reveal comparable studies of chronic over-ventilation at normal oxygen tensions. Several studies (1-6) have been made of electrolyte and water metabolism during short periods of voluntary hyperventilation. The present study was undertaken to ascertain the consequences of prolonged passive hyperventilation in man with particular reference to the composition of the blood and urine. The study was stimulated by the observation that patients maintained in body-type respirators for long periods were frequently hyperventilated. It therefore seemed important to study the basic physiological alterations in prolonged simple passive hyperventilation.

Previous studies of short periods of voluntary hyperventilation in man have shown increased volume, decreased titratable acidity, decreased excretion of ammonia (1, 2) and decreased excretion of phosphates (3) in the urine. Furthermore, decreased CO<sub>2</sub> content, decreased CO<sub>2</sub> capacity, increased pH and decreased inorganic phosphate in the blood have been reported (3, 4, 5). A comprehensive analysis of the blood electrolyte changes with voluntary hyperventilation has been reported by Rapoport *et al.* (6). In these and other previous studies the overventilation was carried out for periods of time ranging from 6 to 90 minutes.

### PROCEDURE

In this study 8 young, healthy, male subjects were hyperventilated in a body-type respirator<sup>2</sup> for periods of 8 or 24 hours. At least 48 hours prior to the beginning of the period of hyperventilation the subjects were placed on a diet consisting of University of Minnesota Hospital Diet II (as described by Varco, 7), milk and water *ad libitum*. This diet was continued until 24 hours after completion of the period of overventilation. Urine samples were saved

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<sup>2</sup> We are indebted to the J. H. Emerson Company for the loan of this equipment.

for the 24 hours before, for the period of hyperventilation, and for the 24 hours after the experimental period. These samples were refrigerated immediately after being voided and analyses were made after the 24-hour or 8-hour sample was completed. No precautions were taken to prevent loss of  $\text{CO}_2$  from the samples.

The ventilation rate employed for a given subject was established by setting the respirator at the subject's normal respiratory rate and increasing the pressure gradient within the respirator until the subject exhibited symptoms of tetany. In every instance this occurred when the ventilation ratio (defined as minute volume divided by the normal resting minute volume) was between 2 and 3. When carpopedal spasm appeared or the subject complained of tingling, drawing, or other skin sensations the pressure gradient was reduced until symptoms abated. An attempt was then made to maintain this ventilation rate during the remainder of the hyperventilation period. Measurements of ventilation rate were made at intervals throughout the time the subject was in the respirator, but these recorded values are sample measurements and do not necessarily represent the average ventilation over the hyperventilation period. After the respirator was stopped and opened, the subject remained resting for one and one half hours while ventilation records were made and the first post-hyperventilation blood was drawn. *Subjects 3, 4, and 5* were hyperventilated 8 hours; the other 5 subjects, 24 hours.

The methods of measuring ventilation and the treatment of arterial blood samples for  $\text{CO}_2$  content and  $\text{CO}_2$  capacity determinations have been described previously (8). Whole blood was used for the  $\text{CO}_2$  content and capacity determinations for the first 5 subjects, and true separated plasma was used for these measurements for the last 3 subjects. Sodium heparin solution in an amount of 0.01 ml/ml. of blood was used as anticoagulant. Since all samples are subject to the same error no correction has been made in the reported analyses for this dilution nor for the addition of sodium, which amounted to 1.8 milliequivalents per liter of blood. Control blood samples were drawn 24 hours before, and usually a second sample 1 or 2 hours before the hyperventilation started. During hyperventilation, 2 to 4 blood samples were obtained, and at 1 hour and 24 hours after stopping the overventilation additional samples were drawn. Only  $\text{CO}_2$  content and capacity were measured on the blood of *subjects 1 and 2*; additional determinations were made in the case of the other 6 subjects as indicated in table 2.

Sodium and potassium concentrations in plasma and urine were determined with the flame photometer<sup>3</sup>, using LiCl as an internal standard (9). The method of Van Slyke (10) was used for chloride determinations, and

<sup>3</sup> The Internal Standard Flame Photometer used was loaned by Dr. R. B. Barnes, Director of Research, American Cyanamid Company. Thanks are due to Dr. W. D. Armstrong and Mrs. Mary Smersh for assistance with the analyses of sodium and potassium.



phosphates were determined by the method of Fisk and SubbaRow (11). Urine acidity was assayed by titration with 0.1N NaOH to a phenolphthalein end point, and urine pH was measured with a glass electrode pH meter. Intake of sodium, potassium, chloride and phosphates in the diet was estimated on the basis of calculations from analyses of aliquots of the milk and University Hospital Diet II.

TABLE 1. AVERAGE HOURLY URINARY EXCRETION FOR THE 24 HOURS BEFORE, FOR THE TIME DURING, AND FOR THE 24 HOURS AFTER PASSIVELY INDUCED HYPERVENTILATION FOR 8 SUBJECTS

	URINE ml.	MILLIEQUIVALENTS TITRATABLE ACID mEq.	pH	Na mEq.	K mEq.	Cl mEq.	P mmol.
Before.....	49.0	2.17	5.7	5.1	3.7	6.1	1.89
During.....	68.0	-0.09	7.7	10.3	5.1	5.6	0.52
After.....	27.8	2.54	5.4	3.3	3.4	3.2	2.10

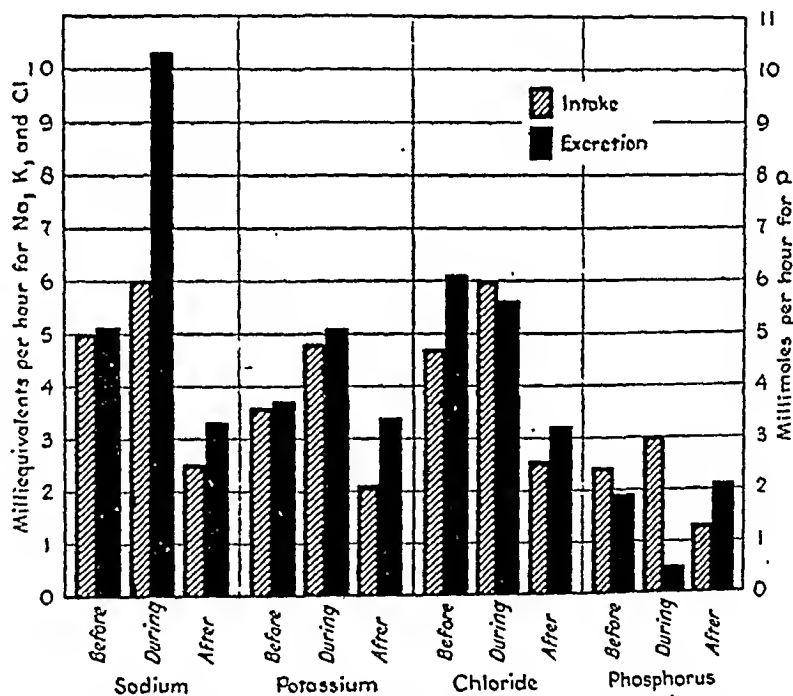


Fig. 1. INTAKE AND URINARY EXCRETION of sodium, potassium, chloride, and phosphorus for the 24 hours before hyperventilation, for the period of hyperventilation, and for the 24 hours following hyperventilation.

## RESULTS

Averages of urinary volume, acid, sodium, potassium, chloride and phosphates excreted per hour before, during, and after hyperventilation are presented in table 1. The diuresis, decrease in acidity and decreased excretion of phosphates reported for short periods of overventilation are also evident here. In addition, a marked increase in excretion of sodium and a smaller

increase in excretion of potassium are shown. The excretion values cannot be interpreted properly without comparison with the simultaneous intakes. Such comparisons are presented in figure 1. If excretion of these electrolytes by other routes remains relatively constant, there would appear to be a significant loss of sodium and a retention of phosphates by the body during prolonged hyperventilation. There is no great change in chloride or potassium balance, although it is possible that a slight retention of chloride occurred during hyperventilation.

Blood data for the 8 subjects are presented in table 2. With the degree of hyperventilation imposed, arterial blood  $\text{CO}_2$  content decreased an average of about 15 per cent in one hour, 25 per cent in 8 to 12 hours, and remained practically unchanged thereafter. One hour after termination of the imposed hyperventilation, the arterial  $\text{CO}_2$  content was still 14 to 16 per cent below normal, and 24 hours after artificial hyperventilation was discontinued the arterial  $\text{CO}_2$  content was still depressed in all subjects.

Although the arterial  $\text{CO}_2$  capacity changes were not consistent from subject to subject during the first hour of overventilation, the average shows a slight increase. From one hour of hyperventilation until some time between one and 24 hours after termination of artificial hyperventilation, the average  $\text{CO}_2$  capacity fell. It should be noted that in the first hour after turning off the respirator, this value decreased in 7 of 8 subjects and in the 8th no change occurred. Changes in  $\text{CO}_2$  content and capacity with time are presented in figure 2. Both the whole blood (first 5 subjects) and plasma (last 3 subjects)  $\text{CO}_2$  capacity curves show a slight rise during the first hour, a steady fall during the remainder of the hyperventilation period and a marked increase in the slope of this fall during the first hour after hyperventilation. Twenty-four hours later,  $\text{CO}_2$  capacity had increased but was still below normal in 7 subjects.

Potassium was measured in the plasma of 2 subjects and no consistent change was found. Rapoport *et al.* (6) found a small but significant increase in the level of serum potassium with 6 minutes of voluntary hyperventilation. They mention increased secretion of adrenalin as a possible explanation for this change in potassium level.

Plasma sodium concentration decreased early in hyperventilation in 4 of 5 subjects. The average fall was 3.8 mEq. per liter during the first hour of hyperventilation. Insufficient data are available to draw conclusions about the behavior of the plasma sodium during the remainder of the experimental period. In subject 3 the plasma sodium level fell steadily during the overbreathing and was still somewhat low 24 hours later. In other subjects the changes were erratic.

Plasma chloride levels showed no consistent change. Three of the five subjects showed a fall in chloride during hyperventilation, a change which is

TABLE 2. VENTILATION RATIOS AND BLOOD ELECTROLYTE CHANGES BEFORE, DURING AND AFTER  
24 HOURS OF PASSIVE HYPERVENTILATION

		VENT. RATIO	CO <sub>2</sub> <sup>1</sup> CON- TENT	CO <sub>2</sub> <sup>1</sup> CAPAC- ITY	PLASMA Na	PLASMA Cl	PLASMA INOR- GANIC P
			mM/l	mM/l	mEq/l	mEq/l	mM/l
Subj. 1 24 hrs.	Before hyperventilation	1.0	20.9	20.6			
	1 hour of hyperventilation	2.5	18.2	22.3			
	24 hours of hyperventilation	2.5	19.5	22.1			
	1 hour after hyperventilation	1.8		20.2			
	24 hours after hyperventilation			18.0			
Subj. 2 24 hrs.	Before hyperventilation	1.0	21.5	21.1			
	1 hour of hyperventilation	2.2	16.5	21.2			
	24 hours of hyperventilation	2.2		18.0			
	1 hour after hyperventilation			18.0			
	24 hours after hyperventilation			20.0			
Subj. 3 8 hrs.	Before hyperventilation	1.0	21.6	21.0	145.6	104.5	1.62
	½ hr. of hyperventilation	1.9	17.8		142.4	104.8	.45
	2½ hrs. of hyperventilation	2.4	16.5	21.4	140.2	106.8	.53
	8 hours of hyperventilation	2.6	15.1	21.5	136.9	108.8	.58
	1 hour after hyperventilation	.96	19.8	18.8		106.3	
	17 hours after hyperventilation	1.1		21.8	143.5	102.4	1.61
Subj. 4 8 hrs.	Before hyperventilation	1.0	22.8	21.6	132.2	103.1	1.48
	½ hour of hyperventilation	2.6	20.0	22.8	133.7	102.2	1.22
	8 hours of hyperventilation	2.8	18.6	20.9	134.4	102.9	1.48
	1 hour after hyperventilation	1.5	19.4	20.1	137.8	107.5	1.87
	23 hours after hyperventilation	1.0	21.2	21.0	130.5	108.1	1.61
Subj. 5 8 hrs.	Before hyperventilation	1.0	22.2	22.3	147.8	104.9	1.84
	½ hour of hyperventilation	2.0	14.5	21.8	139.3	98.9	.61
	8 hours of hyperventilation	2.1	15.1	20.8	147.8	99.7	.81
	1 hour after hyperventilation	1.4	17.8	19.3	141.3	100.1	1.58
	23 hours after hyperventilation	1.2	19.0	20.2	138.9	99.9	1.55
Subj. 6 24 hrs.	Before hyperventilation	1.0	26.9	26.9		108.5	1.28
	1 hour of hyperventilation	2.1	22.8	28.4		109.6	.55
	12 hours of hyperventilation	2.8	20.6	28.3	145.9	125.2	
	24 hours of hyperventilation	2.7	19.8	25.7	139.1	119.8	1.02
	1 hour after hyperventilation	1.5	22.6	25.4	144.6	118.2	1.36
	24 hours after hyperventilation	1.03	22.5	25.6	145.9	106.5	1.35
Subj. 7 24 hrs.	Before hyperventilation	1.0	28.9	29.0	142.2	117.3	1.19
	1 hour of hyperventilation	1.6	25.4	27.1	137.2	108.7	.29
	12 hours of hyperventilation	1.7	18.4	27.4			.63
	24 hours of hyperventilation	2.2	20.2	26.8		115.2	.12
	1 hour after hyperventilation	.87	24.0	26.0	149.1	108.7	1.44
	24 hours after hyperventilation	.90	26.2	27.0	130.0		1.31
Subj. 8 24 hrs.	Before hyperventilation	1.0	26.6	28.1			1.50
	1 hour of hyperventilation	3.4	22.3	28.7			.95
	12 hours of hyperventilation	3.1	20.5	26.5			.86
	24 hours of hyperventilation	2.7	20.2	26.5			1.00
	1 hour after hyperventilation	1.2	22.7	25.3			1.44
	24 hours after hyperventilation	.90	23.0	25.9			1.00

<sup>1</sup> Subjects 1-5 whole blood, subjects 6-8 true separated plasma.

in the direction opposite to that which might be expected as a compensation for the lowered bicarbonate level. In experiments on himself, Peters (12) found a fall in plasma chloride with voluntary overbreathing which he was unable to explain.

The most striking and consistent change observed in plasma electrolyte concentrations, other than bicarbonate, was that of inorganic phosphate. One hour of hyperventilation resulted in an average decrease of 54 per cent, and the plasma level of this anion remained low during the remainder of the overventilation period, returning to normal within the first hour after hyperventilation was discontinued.

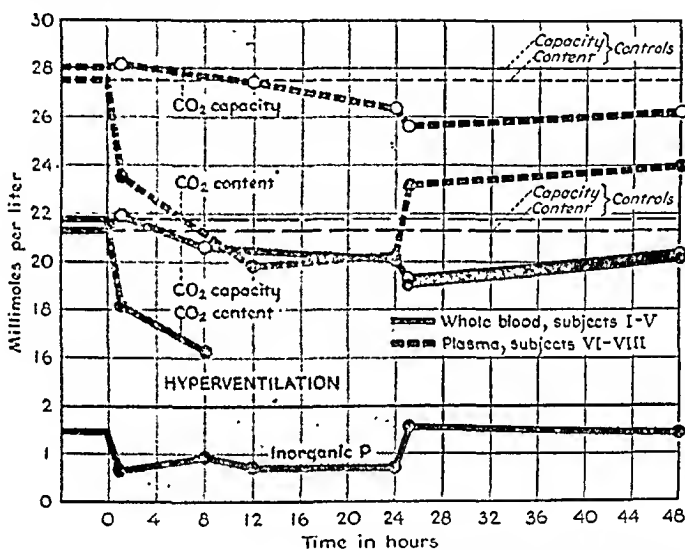


Fig. 2. WHOLE BLOOD AND PLASMA CO<sub>2</sub> CONTENT and capacity, and plasma inorganic phosphorus changes with hyperventilation. The whole blood CO<sub>2</sub> content line is broken between 8 hours of hyperventilation and 1 hour after hyperventilation since no determinations were made on this group of subjects during this interval.

### DISCUSSION

Changes in the composition of the blood and urine with 8 and 24 hours of passive hyperventilation are in general in the same direction as have been reported previously for short periods of intense voluntary hyperventilation. The blood electrolyte changes noted in this study also follow fairly closely those reported for subjects on mountain climbing expeditions or subjects maintained at low atmospheric pressure over long periods in a low pressure chamber. Dill *et al.* (13) at heights up to 6.14 km. in the Peruvian Andes reported a slight increase in serum chloride, decrease in sodium, a marked decrease in bicarbonate, and no change in protein lactate, potassium and calcium. Serum inorganic phosphates were not measured.

In electrolyte balance studies on himself during a stay at high altitude, Sundstroem (4) found an increased excretion of basic elements and a negative balance of base on moving from sea level to high altitude.

In a 10-hour exposure to simulated altitudes of 8,000 and 10,000 feet, D'Angelo (15) found a significant reduction in renal excretion of inorganic phosphates. Subjects maintained at much higher simulated altitudes in a low-pressure chamber and over much longer periods of time showed a rise in blood  $pH$ , which was not compensated during the stay of 36 days in the chamber, a fall in  $CO_2$  capacity and no change in plasma chloride or protein during the exposure (16).

*In vitro* studies on blood indicate that the inorganic phosphate level changes in the same direction as the hydrogen ion concentration (17, 18). The  $pH$  change may be the controlling factor in the inorganic phosphate shift in the intact body. Shifts into both red blood cells and tissue cells may be controlled by this factor. It may also be noted (fig. 2) that the early shifts in alkali reserve, at one hour of hyperventilation and at one hour post-hyperventilation are opposite to later trends and could be accounted for in part at least by the inorganic phosphate changes.

Although hyperpnea following short periods of voluntary hyperventilation has been observed in a small percentage of individuals (19), the usual result of such forced breathing is a period of apnea. Apnea was not observed in any instance, however, following 8 or 24 hours of passively imposed hyperventilation, and in 6 of 8 subjects an increased ventilation persisted for several hours after termination of the artificial hyperventilation. More extensive studies on respiratory reactions after passive hyperventilation on other subjects, to be reported separately, show that a persistent increase in minute respiratory volume is the more regular occurrence. The subjects whose data are reported here were not 'trained' as well before hyperventilation because the studies were not pointed in the direction of measuring the post-hyperventilation respiratory volume response in this series. In this connection it has been shown that there is an increased response to inhaled  $CO_2$  during this period of spontaneous overventilation following 24 hours of passive hyperventilation (8).

A persistent overventilation has regularly been observed when individuals who have had a prolonged exposure to low oxygen tension are returned to normal oxygen tension (20, 21, 22).

Gray (23) has attributed this maintained overventilation to an increase in the sensitivity of the respiratory center to  $CO_2$ .

#### SUMMARY

Eight, healthy young men were hyperventilated in a body type respirator; 5, for 24 hours and 3, for 8 hours. During the hyperventilation there

was an increase in the volume of urine excreted, an increase in the excretion of urinary sodium and potassium, and a reduction in the excretion of phosphates. Little change in excretion of chloride was observed. A comparison of the intake of sodium, potassium, chloride and phosphates with urinary excretion indicates an overall loss of sodium and a retention of phosphates during prolonged hyperventilation.

Of the plasma electrolytes measured, only bicarbonate and inorganic phosphates showed a consistent change with prolonged passive hyperventilation. Inorganic phosphate level fell rapidly with onset of overventilation. Plasma sodium concentrations regularly fell during the first hour of hyperventilation, but later changes were random. The fall in  $\text{CO}_2$  content and capacity accompanying 8 or 24 hours of passive hyperventilation had not been completely repaired in the 24 hours after termination of the hyperventilation.

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# *Effect of Hyper-Immune States on Human Blood Pressure Response to Epinephrine*

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THE PRESENT STUDY owes its origin to a review by Nordmann (1) in 1931, dealing with local reactions in sensitized animals. Nordmann cited evidence obtained by Tonietti (2) and by Dietrich and Nordmann (3, 4) that immunization is accompanied by an alteration in the response of blood vessels to epinephrine. Tonietti measured the response of systolic blood pressure to the intravenous injection of 0.01 mg. of epinephrine before and at intervals after the administration of horse serum intramuscularly in human subjects and found that the blood pressure rise was not as great after the injection of horse serum as it had been before.

Dietrich and Nordmann (3) immunized rabbits intensively with killed colon bacilli given intravenously and then observed microscopically the effect on mesenteric blood vessels of the local application of epinephrine. They found that the constrictor reaction which epinephrine normally elicits was shortened in sensitized animals. In a subsequent paper they (4) further reported that immunization by this method also diminishes the vascular response of rabbits to epinephrine given intravenously: carotid arterial pressure changes were smaller and of shorter duration than in the unsensitized animal, and on microscopic observation of the mesentery it was seen that vasoconstriction did not last as long as in the normal.

These observers were of the opinion that the alterations in epinephrine response were mediated through the central nervous system, on the assumption that sensitization modifies the irritability of that system. It is our belief, on the contrary, that the deviation from the normal vascular response to epinephrine was due to the fixation of antibodies on or in the tissue cells of blood vessel walls. This belief is based on present knowledge of the mechanism of anaphylactic reactions, as outlined in standard texts of immunology (5). It is generally agreed that antibodies are capable of being attached upon or within tissue cells and that it is these tissue-fixed or sessile antibodies which take part in the antigen-antibody union which gives rise to anaphylaxis. Rich and Follis (6) have shown that local anaphylactic reactivity, as exemplified by the Arthus phenomenon, cannot be aroused on the cornea of the rabbit unless a growth of blood vessels has previously been induced upon that ordinarily avascular structure. Abell and Schenck (7) installed transparent moat-chambers in the ears of rabbits and immunized the animals with horse serum. When the same antigen was introduced either into the moat or intravenously, a vigorous contraction of the arterioles was observed.

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From these and other observations it may be inferred that antibodies are fixed on or in the tissue cells of blood vessels, particularly arterioles.

The terms circulating and tissue-fixed antibody will be used more or less interchangeably in speaking of their effect on the blood pressure response to epinephrine. There is reason to believe that a positive correlation exists between the amount of circulating antibody of almost any specificity and the amount of antibody of the same specificity which is fixed in arterioles. Using collodion particles for accuracy of precipitin determinations, Cannon and Marshall (8) have shown a close parallelism between the strength of precipitins circulating in the blood of a given animal and the intensity of the Arthus phenomenon produced by homologous antigen at the same time in that animal. On the reasonable assumption that the Arthus phenomenon is a function of fixed antibody, this parallel implies a sort of dynamic equilibrium between circulating and fixed antibody analogous to that which exists (9) between other plasma proteins and cell proteins generally. The antibody equilibrium however seems to be a special case, by virtue of selective localization in the vascular tree.

During an investigation of rheumatoid (atrophic) arthritis our attention was drawn to this subject by the suspicion that the functional state of peripheral arterioles is an important factor in the pathogenesis of this type of arthritis. The blood pressure observations recorded herein are interpreted as indicating that the presence of a *large* amount of sessile antibody tends to impede the contraction of vasoconstrictor muscle fibers.

#### METHODS

Preliminary experiments showed that the subcutaneous administration of epinephrine caused a blood pressure rise which was too gradual for our purpose, and this route was abandoned in favor of the intravenous. In the hope of avoiding the instability of epinephrine in dilute solution, a trial was also made of Neo-synephrine intravenously, but this drug proved inadequate as a sensitive indicator of vasoconstrictor activity, presumably because, unlike epinephrine of natural origin, it contains no depressor component (10, 11). The blood pressure rise produced by epinephrine given intravenously is apparently the resultant of a conflict between vasodilation (12) and vasoconstriction. With epinephrine, a relatively slight weakening of either of these forces will thus be demonstrable because of the tendency of the other to predominate. In the absence of a vasodilator component, as in the case of Neo-synephrine, a slight weakening of vasoconstriction could fall within the range of experimental error and so pass undetected.

*Epinephrine Test.* From the technique of Kraines and Sherman (13), who gave 0.01 mg. of epinephrine intravenously in a study of psychoneurosis, we adopted a preliminary intravenous injection of physiologic salt solution, which serves both to accustom the subject to the procedure and to aid the observer in evaluating the psychic component in each individual's response. The saline was omitted when the test was subsequently repeated on the same individual. A fresh dilution of epinephrine in saline, to contain 0.01 mg. in 1.0 cc., was made for each day's tests. Four stock bottles, bearing the same lot number, provided all the 1:1000 epinephrine used in these experiments.

The test was conducted in the following manner. With the subject re-



cumbent, the cuff of a mercury manometer was applied to one upper arm and the other elbow was exposed for injections. Upon repetition of the test the same arm was always used for the cuff. The blood pressure readings in the earlier experiments were all made by one observer (*E.P.*) and the remainder by another (*S.M.II.*). Since epinephrine had no constant effect on the diastolic phase, systolic pressures alone are recorded herewith. When the blood pressure had become stabilized with recumbency, 1.0 cc. of physiologic salt solution was injected with a tuberculin syringe and 26-gauge needle into an antecubital vein over an interval of 50 seconds. To help keep the rate of injection even, an assistant called out the time in multiples of 5 seconds. In apprehensive individuals this injection often caused a small rise in systolic pressure, usually not exceeding 4 mm. Hg and lasting less than a minute. In phlegmatic persons no effect was apparent. The subsequent base level was often a little lower than before, attributable to relief at completion of an injection. One cc. of epinephrine 1:100,000 (0.01 mg.) was then given similarly and blood pressures recorded. Near the end of the injection, the plunger of the syringe was pulled back briefly, for assurance that the needle was still in the vein. The subject was not told that the second injection differed from the first. Conversation on his part was discouraged from the first injection to the completion of the experiment, inasmuch as sick subjects usually wanted to discuss their illness, a topic which was apt to produce a slight rise in blood pressure. There was often a rise of 2 to 4 mm. in systolic pressure as the subject watched the preparation of syringes. At the close of the experiment, venous blood was withdrawn if needed for additional studies and the subject was asked to describe the sensations aroused by the injections.

The value of the preliminary injection of saline and the occasional difficulty in satisfactory placement of the base line or resting level are illustrated in figures 7 to 10. The drop following the saline injection in figure 7 obviously represents relief. In this individual, anticipation obscured the true resting level. The rise before the saline injection in figure 8 occurred as the subject watched the preparations for the injection. In selecting a base line for each experiment we usually chose the lowest value which was obtained at least twice at any time before the injection of epinephrine. This seemed more reliable than the reading immediately before this injection, which often reflected slight anticipation. In some individuals the lowest reading of the whole series was the first one, at the beginning of the experiment, before the subject fully realized what was going to be done. Occasionally an individual was encountered whose systolic pressure was too labile to permit the establishment of an acceptable base line under the circumstances of the experiment (fig. 9). For this reason, and because part of the rise following epinephrine in such a person is probably of psychic origin, results of this sort are difficult or impossible to interpret and have been discarded. Figure 10 shows psychic

effects of equal range but more regularity. Here interpretation is less difficult. It has seemed to us that apprehension and lability of blood pressure are more apt to occur in the male.

We have not found a satisfactory basis on which to calculate dosage for individuals below adult levels in age or weight and for this reason children were not used as subjects. As a matter of fact, it is likely that in the case of pressor effects of epinephrine given intravenously, the exact dosage is relatively unimportant, provided very small doses are avoided. This paradox may be attributed to the compensatory effects both of the depressor component in epinephrine of natural origin and of the protective reflexes which attempt, through increased activity of vagal and vasodilator mechanisms, to return the cardiovascular status to normal (14). Thus, Freeman and Carmichael (15) obtained a mean systolic rise of 56 mm. Hg on giving 0.05 mg. or 5 times our dosage to normal men, and in Hume's (16) subjects an intravenous dosage of 0.15 to 0.3 mg. produced disturbances of cardiac conduction but gave systolic pressures rises of the order of only 40 mm. Hg.

In selecting subjects for the epinephrine test, the following were excluded: individuals with a resting systolic pressure above 140 mm. Hg (with rare exceptions), serious heart disease, definite pulmonary cavitation, a surgical procedure within the previous week or a history of cerebral vascular disease.

*Heterophile Antibodies.* The technique of Paul and Bunnell (17) was followed, except that room temperature overnight was substituted for the 38° C. bath and refrigeration. The results are recorded in terms of the final serum dilution. Reading with the unaided eye, the last tube with barely perceptible but definite agglutination was taken as the end point.

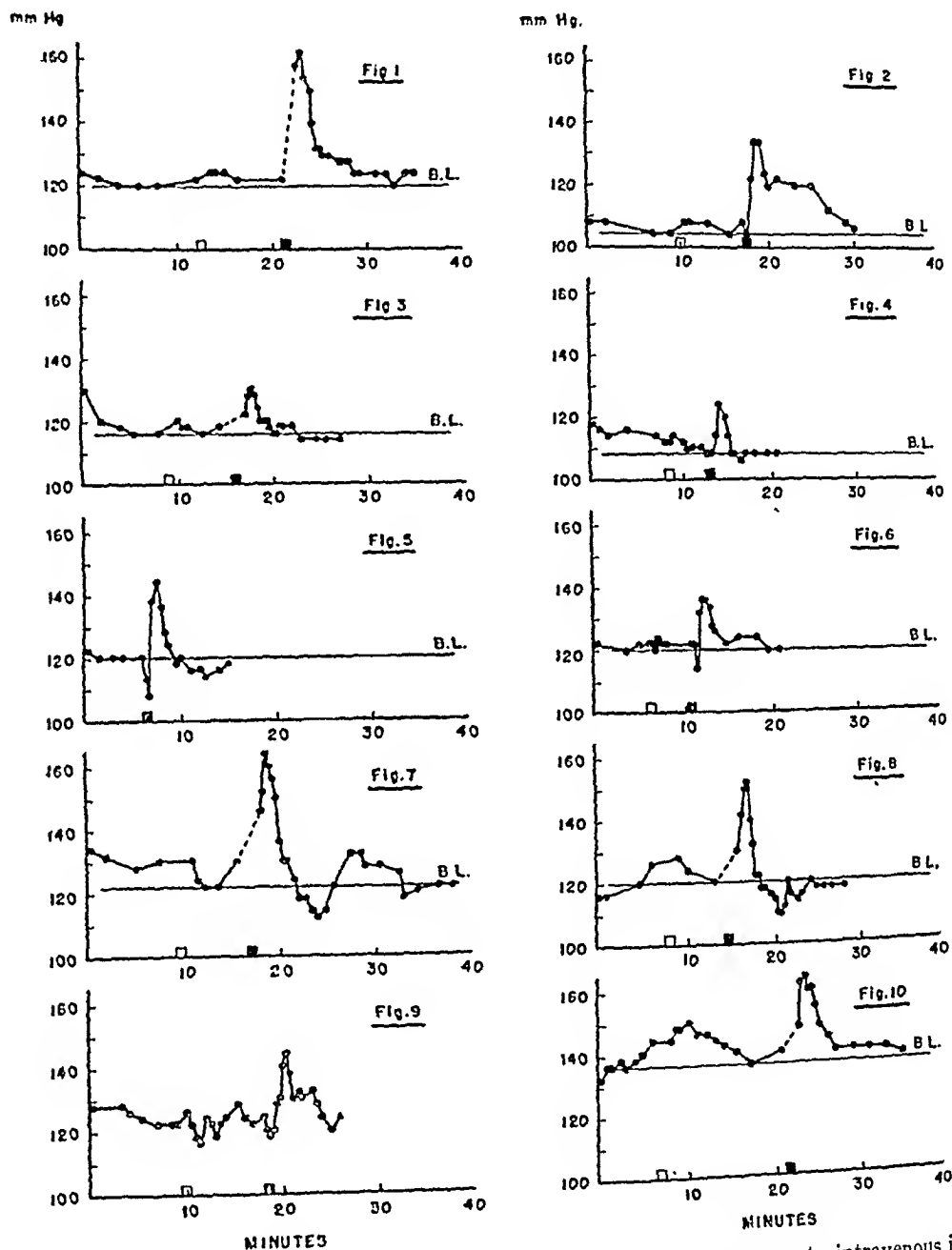
*Serum Proteins.* These determinations were performed by Miss Hester Snider, through the courtesy of Dr. John G. Reinhold, to both of whom our thanks are due. The procedure used was the biuret method of Kingsley (18).

## RESULTS

### *General Observations*

Characteristic blood pressure responses to the intravenous injection of 0.01 mg. of epinephrine are detailed in figures 1 to 10. Figures 1 and 2 show typical large rises and figures 3 and 4 typical small rises in systolic blood pressure. Depressions below the base line, occurring either before the peak of epinephrine response (primary reversal) or after it (secondary reversal) may be seen in figures 5 to 8. Primary reversals, which were more common than secondary, usually consisted of depressions of 4 to 8 mm. Hg below the base line, with an extreme of 12. They usually occurred during the latter half of the epinephrine injection (figs. 5 and 6) and would therefore be missed unless blood pressure determinations were made while the injection was in progress. They were found in about half the instances in which readings were taken

during this time. It is likely that the actual incidence was higher than this, as primary reversals are fleeting and small ones could easily be missed. The



Figs. 1-10. REPRESENTATIVE SYSTOLIC BLOOD PRESSURE RISES in response to intravenous injection of 0.01 mg. of epinephrine. Open square=injection of salt solution; solid square=injection of epinephrine; B.L.=base line. Additional preliminary rest periods of 10 minutes or longer are not shown.

observations of Wiggers, Duschatko and Kory (19) suggest that the primary reversal may be due to dilatation of pulmonary vessels or of the aorta and its immediate large branches, or both. We found no constant relation between

primary reversal and any other feature of the blood pressure curve. Primary reversals in fact vary for the same individual on repeated tests, probably owing in part to the discontinuous method of observation.

The less frequent secondary reversal (figs. 7 and 8), occurring after the principal peak, is attributable to peripheral action of the depressor component of the drug (12). Goodman and Gilman (14) point out that the effect of this component is more prolonged than that of the pressor component. Why a secondary reversal should occur only on occasional tests is not clear. Sometimes, as in figure 7, it is followed by a secondary smaller rise and this in turn by another still smaller reversal. When a secondary reversal did not occur, its place was usually occupied by the interruption of the downward curve by a shoulder or sloping plateau (figs. 1 and 2), which may represent the release of sympathin E. Of the various deviations in systolic pressure which are produced by epinephrine, the classical rise was the only one which was found consistently in all our experiments.

There was considerable variation in the intensity of the sensations evoked by epinephrine. The more common of these, in order of diminishing frequency, were: palpitation, nervousness, warmth and tingling (particularly of the face and scalp), fulness in the head, generalized weakness and a feeling of swelling in the lower extremities. The subjects described their sensations with such phrases as: "felt hot and bothered," "felt like I had just been running," "as if I had been caught doing something to be ashamed of" or "my knees turned to water." Most subjects upon retesting reported the same sensations as before, but of smaller intensity, presumably because appreciation was dulled by familiarity. There appeared to be no constant relation between the intensity of the subjective phenomena and the height of the blood pressure rise. A few deep breaths during the latter part of the injection of epinephrine indicated a slight respiratory stimulation. This was very common and bore no relation to the intensity of sensations. An increase in pulse rate usually occurred just prior to the rise in pressure.

Retesting of individuals at 30-minute intervals yielded results which were consistent within  $\pm 4$  mm. Hg. A comparable range was observed by Cameron (20) when he repeated the test at 10-minute intervals, using a dosage similar to that employed herein. These variations are understandable when one recalls that the blood pressure rise is the resultant of a number of forces, including pressor and depressor effects exerted over a large area of the vascular tree, sensitive and subtle reflex compensatory mechanisms and a psychic component of unknown and variable intensity.

The results obtained in a group of 41 individuals, both sick and well, are presented in table 1. No correlation was observed between age, sex, race, weight or resting systolic pressure and the height of the blood pressure rise induced by epinephrine.

TABLE 1. SYSTOLIC BLOOD PRESSURE RISES IN RESPONSE TO EPINEPHRINE

	SEX AND COLOR	AGE	WT.	HT.	EPINE- PHRINE	BLOOD PRESSURE			DIAGNOSIS
						Base line	Rise with epine- phrine	Second- ary reversal <sup>1</sup>	
		yr.	lb.	in.	mg.	mm.Hg	mm. Hg	mm. Hg	
1	F C	25	134	65	0.01	84	56		Sarcoidosis, improving
2	M W	32	161	72	0.01	120	42		Slight wound infection, 7 days
3	M W	55	138	66	0.01	122	42	-10	Diabetes mellitus—minor foot infection
4	F C	15	180	62	0.01	120	42		Hip cast, slipped epiphysis—bed 1 month
5	M W	45	130	63	0.01	132	40		Laparotomy 14 days ago
6	M C	21	140	67	0.01	120	40		Sickle cell anemia
7	M W	44	160	68	0.01	128	36		Fract. femur—bed 1 yr—out briefly recently
8	M C	18	183	71	0.01	134	36		Herniorrhaphy 6 days ago
9	FW	23	117	65	0.01	108	36		Apparently normal
10	FW	16	134	67	0.01	120	34		Convalescent virus pneumonia
11	FW	40	161	65	0.01	120	32	-10	Tube in common duct
12	M C	71	140	66	0.01	104	30		Tumor of sternum
13	M W	56	122	67	0.01	120	30	-6	Psychoneurosis
14	F C	29	111	66	0.01	100	30		Sarcoidosis, improving
15	FW	25	130	60	0.01	122	28		Apparently normal
16	M W	50	153	67	0.01	136	28		Diabetes mellitus—minor foot infection
17	FW	32	125	64	0.01	112	28		Chronic osteomyelitis of femur
18	M C	16	70	65	0.005	102	26		Ulcerative colitis
19	M W	72	133	68	0.01	106	26		Subsiding jaundice
20	FW	36	165	65	0.01	106	26		Possible kidney stone
21	M W	42	175	73	0.01	122	26		Apparently normal
22	M W	18	160	69	0.01	116	24		Bedfast 3 months since hip fusion
23	M W	36	155	66	0.01	116	24		Apparently normal
24	M W	60	150	66	0.007	136	22		Possible carcinoma of stomach
25	M W	26	150	72	0.01	122	20		Chronic glomerulonephritis
26	M C	38	145	71	0.01	122	18		Possible arthritis of hip
27	M C	41			0.01	116	18		Ankylosing spondylitis
28	FW	70	85	67	0.007	120	18		Carcinomatosis with cachexia
29	M W	56	176	71	0.01	120	18		Polycythemia—pneumonitis
30	M W	16	143	64	0.01	122	16		Study—diarrhea
31	M W	14			0.005	110	16		Residual poliomyelitis—bed 4 months
32	M W	45	144	68	0.01	102	16		Fract. skull and tibiae 6 weeks ago
33	M W	61	150	70	0.01	104	16		Gastric resection 8 days ago
34	M W	26	153	69	0.01	110	16	-6	Recurrent colitis
35	FW	15	130	68	0.007	118	14	-8	Appendectomy 8 days ago
36	M W	33	160	64	0.01	116	14		Probable septicemia
37	M W	34	125	65	0.01	110	14		Chr. osteomyelitis—exacerba- tion 2 weeks
38	M W	14	100	61	0.005	112	14		Convalescent acute rheumatic fever
39	M W	40			0.01	102	14		Study—unexplained weight loss
40	M W	60	155	68	0.01	120	14		Bronchopneumonia, 9th day
41	M W	41	142	66	0.01	122	10		Hydronephrosis

Mean.....

25.6 ± 1.65 S.E.

<sup>1</sup> Where a secondary reversal is not noted, none occurred.

### *Hyper-Immune States*

In order to arouse an antibody response and follow its effect on the blood pressure rise produced by epinephrine, booster injections of typhoid vaccine were given to 3 subjects. The resulting Widal titers did not exceed 1:320 and a depression of epinephrine responsiveness was not obtained, presumably because antibodies were not aroused in sufficient numbers.

A depression of epinephrine responsiveness was found however in subjects with rheumatoid arthritis or infectious mononucleosis, conditions in which antibodies appear to be present in excessive numbers.

*Rheumatoid Arthritis.* It has been shown elsewhere (21) that the tendency toward reversal of the albumin-globulin ratio which exists in the sera of patients with active severe rheumatoid arthritis is due principally to an increase in gamma globulin. Such an increase is strong presumptive evidence that antibodies are present in large numbers, although actual demonstration of antibodies in rheumatoid arthritis must await discovery of the antigen which is responsible for their existence and which will unite specifically with them.

The results of epinephrine tests of patients with rheumatoid arthritis are presented in table 2, together with other data including some serum albumin-globulin ratios and an evaluation of the severity of the arthritis. Serum proteins were determined on samples drawn usually on the same day as the epinephrine test, rarely more than 2 days distant from it. In the selection of subjects, cases in which there might be a question of the diagnosis of classical rheumatoid arthritis were excluded. All subjects in table 2 had a fairly symmetrical involvement of the proximal interphalangeal joints of the fingers and a disease duration of at least one year. They are divided into groups according to the intensity of the disease process. Within each group the results are arranged in order of diminishing blood pressure response. It will be seen that the height of this response tends to vary inversely with the activity of the disease, which was estimated on the basis of pain, local heat, swelling, tenderness and, when available, a recent erythrocyte sedimentation rate. It was our impression that the extent as well as the degree of joint involvement was a factor in depressing the response to epinephrine.

It is noteworthy that A-G ratios are significantly lower in *group III*. In view of the above-cited explanation of low A-G ratio in rheumatoid arthritis this relation lends support to the thesis that a depression of epinephrine responsiveness results from the presence of large numbers of antibodies.

A secondary reversal of blood pressure, i.e., a transient fall below the base line following the classical rise, occurred more frequently in persons with rheumatoid arthritis (table 2) than in those without (table 1). The significance of this difference is not known.

*Infectious Mononucleosis.* An investigation of the effect of infectious mononucleosis on blood pressure response to epinephrine was undertaken be-

TABLE 2. SYSTOLIC BLOOD PRESSURE RISE IN RESPONSE TO 0.01 MG. EPINEPHRINE IN PATIENTS WITH RHEUMATOID ARTHRITIS

	AGE	DURATION OF DIS.	BLOOD PRESSURE				A/G	ACTIVITY OF DISEASE	EXTENT OF DISEASE
			Base line	Rise with ea-line	Rise with epinephrine	Secondary reversal <sup>1</sup>			
	yr.	yr.	mm. Hg	mm. Hg	mm. Hg	mm. Hg			
<b>GROUP I</b>									
1 Hag	44	21	128	0	38	-8	2.3	Inactive	Chiefly hands
2 Pol	51	6	110	0	32		2.1	"	Moderate
3 Guc	35	15	104	—	30	-14		"	Widespread
4 Win	47	6	150	36	30 <sup>2</sup>		1.5	Questionable	Hands
5 Cos	65	20	160	4	26	-18	2.5	Inactive	Widespread
6 Har	44	3	112	0	20		1.8	"	Chiefly hands
<b>GROUP II</b>									
1 Sow	60	7	134	16	60 <sup>2</sup>		1.9	Slight	Moderate
2 Voy	33	3	110	0	40 <sup>2</sup>			"	"
3 Szk	45	3	120	4	36 <sup>2</sup>		1.7	"	Slight
4 Aur	23	1	102	4	24		1.9	"	Moderate
5 Kos	52	8	154	8	22	-12		"	Slight
6 Ole	19	10	112	4	22	-4		"	Chiefly hands
7 Sch	36	1	106	2	18		2.1	"	"
8 Lyo	22	3	120	0	12			"	Moderate
<b>GROUP III</b>									
1 Kra	50	4	120	0	32 <sup>2</sup>	-12	1.3	Moderate	Moderate
2 Cha	50	4	126	6	24	-4		Slight	Extensive
3 Boo	51	6	116	6	22	-4	0.9	Moderate	Widespread
4 Lud	46	1	110	12	20 <sup>2</sup>		1.1	"	"
5 Idd	18	2	110	4	16			"	"
6 Mau	38	1	116	0	14	-16	0.8	Marked	"
7 Poo	55	10	110	0	14	-4	1.8	Slight	"
8 Wil	47	1	98	0	14		1.4	Moderate	"
9 Smi	45	1	114	4	12			"	Moderate
10 Shi	45	8	122	2	12	-6		"	"
11 Cla	44	6	120	2	12		1.6	Slight	Widespread
12 Fry	62	14	120	0	12	-18	1.4	"	"
13 Fle	62	1	100	4	10	-10	0.9	Moderate	Moderate
14 Hos	20	3	110	0	10		1.4	Slight	Widespread
15 She	51	1	128	10	10		0.9	"	"
16 Lap	23	3	118	0	10		1.4	Moderate	"
					Blood pressure rise with epinephrine		A/G		
					mean	S.E.	mean	S.E.	
Groups I and II combined . . . . .					30 mm. Hg	±3.3	1.98	±0.10	
Group III . . . . .					15	±1.7	1.24	±0.09	

<sup>1</sup> Where a secondary reversal is not noted, none occurred.<sup>2</sup> These subjects were unusually apprehensive.

cause this disease calls forth numerous (heterophile) antibodies whose strength is easily measurable.

Convalescent patients were made available through the cooperation of Dr. William B. Kennedy, chief of medicine of the Student Health Service of the University of Pennsylvania, to whom our thanks are due. In each of these patients a tentative diagnosis of possible or probable infectious mononucleosis had been made, on the basis of lymphadenopathy and an increase in circulating mononuclear cells. In all instances in which the subject was available for a sufficient period, his convalescence was marked, sooner or later, by subnormal responsiveness to epinephrine (table 3). In the last 2 cases of the table the absence of heterophile antibodies beyond the upper normal limit of 1:32 failed to substantiate the clinical diagnosis. Presumably these 2 subjects had a similar disease whose relationship to infectious mononucleosis remains to be clarified. Their lowered epinephrine response despite the lack of strong heterophile antibodies suggests that they did have numerous antibodies of some other specificity.

#### DISCUSSION

Because of inherent minor inaccuracies of a technical nature (missed peaks, difficulties in placement of base line) and because of the uncertainty introduced by the psychic factor it is evident that deductions from results of this test must be based on *trends* rather than on absolute numerical values. A single result has little significance unless it forms one of a comparable group all tending in the same direction. The trend which emerges from our observations suggests that when a subject possesses antibodies in large numbers his blood pressure response to epinephrine will be below 16-20 mm. Hg. Low values gain additional significance from the fact that psychic influences tend to increase rather than diminish the blood pressure response.

States in which antibodies are present in excessive numbers have been referred to as hyper-immune, for lack of a better term. Immunization to this degree is relatively infrequent in human disease processes and its artificial induction is not always easy and safe. A hyper-immune state was undoubtedly produced by Dietrich and Nordmann (3, 4) in their experimental rabbits. These animals were intensively immunized by the intravenous route, receiving maximal doses of vaccine at 4-day intervals for 5 to 14 doses, a regime which caused the death of some of the animals.

Evaluation of the results obtained by Tonietti (2) in human subjects is difficult. Analysis of his data suggests the possibility that tissue-fixation of the *antigen* (horse serum) was a contributory factor in altering the blood pressure response to epinephrine. For this reason, foreign serum would seem to be an unsuitable antigen for use in investigation of this problem.

The question may be raised whether other aspects of disease, beside the presence of antibodies in large numbers, may have significantly influenced our results. Prolonged bed rest does not of itself lower the blood pressure response to epinephrine (table 1). Toxemia may influence it slightly, but its effect is



minor compared to that of hyper-immune states. Many of our smallest rises were obtained in persons who considered themselves entirely normal.

TABLE 3. SYSTOLIC BLOOD PRESSURE RISES IN RESPONSE TO 0.01 MG. EPINEPHRINE DURING CONVALESCENCE FROM INFECTIOUS MONONUCLEOSIS AND SIMILAR DISEASES

SUBJECT									
<i>New</i> ; female, 20	Day of dis.....	58	95	122					
	BP rise.....	14	16	22					
	Het AB 1:.....	128	16	16					
<i>Spa</i> ; female, 19	Day of dis.....	7	42	56	68				
	BP rise.....		14	18	20				
	Het AB 1:.....	128	16	16	0				
<i>Han</i> ; male, 20	Day of dis.....	14	21	26	30	35	40	49	
	BP rise.....	10	14	20	22	24	34	22	
	Het AB 1:.....	128		8	8				
<i>Pag</i> ; male, 22	Day of dis.....	8	34	49	92	137	167		
	BP rise.....	38	14	18	16	10	14		
	Het AB 1:.....		64	64	16	32	32		
<i>Eva</i> ; male, 23	Day of dis.....	55	62	69	76	97	125	160	177
	BP rise.....	24	8	16	14	16	14	20	14
	Het AB 1:.....	256	128	128	128	64	64	32	16
<i>Hut</i> ; male, 24	Day of dis.....	19	34	39	89				
	BP rise.....	24	14	16	20				
	Het AB 1:.....	1024	256	256	64				
<i>Sis</i> ; male, 23	Day of dis.....	11	18	25	32	39			
	BP rise.....	34	32	30	28	18			
	Het AB 1:.....	64	256	256	128	128			
<i>Str</i> ; male, 23	Day of dis.....	10	17	24					
	BP rise.....	32	30	22					
	Het AB 1:.....	2048	2048	1024					
<i>Cup</i> ; male, 21	Day of dis.....	18	25	32	39	60	67		
	BP rise.....	6	12	14	14	20	24		
	Het AB 1:.....	0		8	16	8	0		
<i>Was</i> ; male, 21	Day of dis.....	5	10	18					
	BP rise.....	20	12	16					
	Het AB 1:.....	0	0	0					

Heterophile antibodies (Het AB): 0 = negative at 1:8, the lowest dilution tested.  
Blood pressure rise in mm. Hg.

It is worthy of note that there was a delay in the appearance of diminished responsiveness to epinephrine in individuals with strong heterophile antibodies

who came under observation soon after the onset of their disease. We believe that the failure of the heterophile antibodies of early *severe* infectious mononucleosis to depress the epinephrine response is related to the *quality* of the antibodies concerned. There is evidence that, as immunization progresses, changes may occur in the physical or chemical properties of the antibodies being formed, changes which are essentially unrelated to their serologic specificity. Joffe (22) found a shift of the isoelectric point of rabbit antibody in the direction of a more alkaline *pH* during the course of immunization, without alteration of specificity and independent of fluctuations in titer. Rosenheim (23) reported that typhoid H agglutinins obtained after the first course of immunization of horses were susceptible to digestion by pepsin, whereas those secured after subsequent courses were resistant to pepsin, without relation to changes in titer. One of the peculiar aspects of infectious mononucleosis is the rapidity of the appearance of large numbers of antibodies in the circulation. The heterophile antibodies which are released early in the course of severe infectious mononucleosis may be deficient in some respect which, without interfering with their specificity, renders them less capable of being fixed to tissue cells. The decreased epinephrine response early in a mild form of this disease or late in convalescence from a severe attack suggests that more leisurely production provides antibodies which are more readily capable of becoming sessile.

Upon consideration of several possible mechanisms by which tissue-fixed antibody might be able to diminish the blood pressure response to epinephrine, it seems probable that their action is on the vasoconstrictor muscle cells rather than on the drug. We visualize sessile antibody as exerting an effect on the surface of these cells, tending by a 'brake-like' influence to retard their responsiveness to epinephrine.

The possibility exists that sessile antibody causes a partial constriction of arterioles, consequently leaving a smaller margin of responsiveness to epinephrine. However, this would imply an elevation of resting blood pressure to levels which we have not found in immunized individuals. On the other hand, if sessile antibody diminishes the responsiveness of vasoconstrictor muscles, it might be expected that an accumulation of sessile antibody would result in a lowering of resting blood pressure, but this likewise has not been encountered. Such an effect is probably minimized by the compensatory mechanisms which regulate blood pressure. Bozler (24) has expressed the opinion that smooth muscle is plastic rather than elastic, i.e., that smooth muscle fibers are capable of re-acquiring their initial tension after changes in fiber length, an ability not possessed by voluntary muscle. The implication of this in the present connection is that vasoconstrictor fibers whose contractile properties have been altered by the presence of sessile antibodies may by molecular re-orientations adjust themselves to the state of tonus required for the maintenance of blood pressure at its previous level. The present test has proved useful for our pur-

pose presumably because the pressor effect of epinephrine is over before such rearrangements can take place in the internal structure of arteriolar constrictor fibers.

### SUMMARY

The observations of Dietrich and Nordmann in animals, indicating that hyper-immunization decreases the responsiveness of blood vessels to epinephrine, are confirmed in human subjects. Despite uncertainties due to the susceptibility of blood pressure to psychic stimuli, trends emerge when the rise in systolic pressure produced by the intravenous injection of this drug is measured in a number of subjects in various stages of immunity and non-immunity. Provided the subject's antibody-producing apparatus has not been recently and strongly stimulated, the intravenous administration of 0.01 mg. of epinephrine, under standard conditions, causes a brief rise of systolic pressure of the order of 20 to 40 mm. Hg. If, on the other hand, antibodies are present in excessive numbers, the epinephrine response is apt to be of the order of 10 to 16 mm. Hg. This effect is unrelated to the serologic specificity of the antibodies.

Diminished responsiveness to epinephrine has been found most consistently in rheumatoid arthritis and infectious mononucleosis, diseases in which antibodies are apparently produced in unusually large amounts.

In the light of existing evidence which indicates that antibodies may become attached to the tissue cells of blood vessels, particularly arterioles, in direct ratio to the quantity of circulating antibodies, these observations suggest that immune states depress the responsiveness of blood pressure to epinephrine through the agency of tissue-fixed or sessile antibody attached to the vessel walls. The molecules of sessile antibody presumably achieve this effect by interfering with the rapid contraction of vasoconstrictor muscle cells.

In infectious mononucleosis the epinephrine response is depressed early following mild forms of the disease and late following severe attacks. This paradox is explainable by the assumption that in the early stages of severe cases, heterophile antibodies are made and released so rapidly that their structure is defective in some respect which, without affecting serologic specificity, renders them less capable of being attached to tissues. Late in convalescence, more leisurely production of antibodies presumably permits this defect to be remedied and the epinephrine response becomes depressed.

### CONCLUSIONS

The fixation of large numbers of antibodies in the walls of arterioles impedes rapid contraction of the arteriolar constrictor muscles. Not all antibodies are equally capable of becoming tissue-fixed.

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